

*FDA CTP - Third Party Governance of Industry-Sponsored
Tobacco Product Research: A Public Workshop*

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A Matter of Record
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Min-U-Script® with Word Index

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1 P R O C E E D I N G S
2 (8:30 a.m.)
3 Welcome and Overview
4 Introduction of Workshop Moderator
5 DR. ASHLEY: Good morning. If you guys
6 could take your seats, that would be great.
7 Welcome to the first day of FDA's public
8 workshop on Third-Party Governance of Industry-
9 Sponsored Tobacco Product Research. My name is
10 David Ashley. I'm the director of the Office of
11 Science here at CTP, and it is my honor and
12 privilege to introduce Mitch Zeller, CTP's new
13 center director, who will be delivering our
14 welcoming remarks.
15 DR. ZELLER: David knows I'm not a doctor,
16 and I don't play one on TV, either.
17 Let me start by welcoming everyone to this
18 public workshop on Third-Party Governance of
19 Industry-Sponsored Tobacco Product Research. And I
20 want to sincerely thank everyone for their
21 participation in today's and tomorrow's
22 proceedings.

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1 This is an issue near and dear to my heart.
2 I've worked on it for the past 10 years, going back
3 to the first public session a group of us held on
4 the topic following the SRNT meeting in New Orleans
5 in 2003. And just for the record, that was a
6 public meeting, and it included participation from
7 the tobacco control and research communities as
8 well as the tobacco industry.
9 Since then, many of us in this room have had
10 smaller gatherings to explore governance issues and
11 examine funding and governance models from non-
12 tobacco sectors. I've also worked with some of you
13 here on a publication that articulated a set of
14 criteria to evaluate potential funding models, and
15 then applied those criteria to several models to
16 see how the models and the criteria held up. And
17 that paper appeared in tobacco control back in
18 2009.
19 There is no escaping the fact that this is a
20 contentious issue between various sectors, from
21 tobacco control and public health groups to the
22 tobacco industry. It's contentious in part because

<p style="text-align: right;">Page 5</p> <p>1 there remains significant trust issues for many in 2 tobacco control and public health, given the 3 historical behavior of the tobacco industry. 4 This workshop is not designed to address or 5 resolve those trust issues, but those trust issues 6 exist, and we all have to be aware of them when 7 we're gathering to talk about the most appropriate 8 governance structure for tobacco product research, 9 especially research to be conducted by tobacco 10 companies. 11 A lot has been said about the word 12 "stakeholder" in the context of CTP's regulatory 13 responsibilities broadly, and especially as regards 14 the topic of this workshop. And I understand the 15 sensitivities here. 16 For me, the key part of the word stakeholder 17 is stake. Many different parties and sectors of 18 society have a stake in whatever governance 19 structure is established. That structure will 20 guide the research needed to create the regulatory 21 science base upon which CTP will make policy, craft 22 guidance and regulations, and evaluate sponsors'</p>	<p style="text-align: right;">Page 7</p> <p>1 share your insights and perspectives, and just as 2 important, it's an opportunity for CTP to listen 3 and to learn. And as much as I'd like to, I'm not 4 going to be able to stay for today's and tomorrow's 5 sessions, but I will follow it with great interest 6 in the days and weeks to come. 7 With that, I want to wish you all the best 8 of luck for what I am certain will be a productive, 9 provocative, and stimulating two days. Thank you 10 all. Have a great meeting, and let me turn it back 11 to David. 12 (Applause.) 13 DR. ASHLEY: Again, welcome to everyone. 14 Glad you are here. Our hope is that this workshop 15 will be a step forward in addressing CTP's need for 16 reliable, accurate, dependable data upon which we 17 must rely to make regulatory decisions. 18 Family Smoking Prevention and Tobacco 19 Control Act required FDA to consult with the 20 Institute of Medicine on the development of 21 regulations or guidance on the scientific evidence 22 required for assessment and ongoing review of</p>
<p style="text-align: right;">Page 6</p> <p>1 applications. And the reality is that it will be 2 the tobacco companies who will be submitting 3 applications under Section 911 of the Tobacco 4 Control Act for MRTP orders. The law provides for 5 that regulatory pathway, and the sponsors are 6 entitled to know the rules of the road. 7 But the issues embedded in Section 911 are 8 complex. Given the history of the marketing of 9 products bearing descriptors such as light and low- 10 tar, Congress made clear that Section 911 had 11 multiple purposes. Yes, it is the pathway for FDA 12 to issue MRTP orders based on a sufficient science 13 base. And we're here today and tomorrow to explore 14 governance structures in that context. But 15 Section 911 is also the provision designed to keep 16 potentially misleading MRTP claims off of the 17 market. The Center has the responsibility to hear 18 from all interested parties on the governance 19 issues, and this workshop is the first step in that 20 process. 21 The workshop is really important. It 22 represents a key opportunity for all of you to</p>	<p style="text-align: right;">Page 8</p> <p>1 modified-risk tobacco products. Specifically, 2 Section 911 of the Act states, "The regulations or 3 guidance issued under paragraph 1 shall be 4 developed in consultation with the Institute of 5 Medicine and with the input of other appropriate 6 scientific and medical experts on the design and 7 conduct of such studies and surveillance." 8 Now, the Institute of Medicine published 9 their report, titled Scientific Standards for the 10 Studies on Modified-Risk Tobacco Products, in 11 December of 2011. The purpose of this public 12 workshop is to discuss Recommendation 10 in the IOM 13 report regarding the governance of studies, which 14 states that, "MRTP sponsors should consider use of 15 independent third parties to undertake one or more 16 key functions, including the design and conduct of 17 research, the oversight of specific studies, and 18 the distribution of sponsor funds for research. 19 Such independent third parties should be approved 20 by the FDA in advance of the research." 21 Now, we have invited interested parties, 22 including regulated industry, with a range of</p>

<p style="text-align: right;">Page 9</p> <p>1 different perspectives on this issue to describe 2 their experiences and offer their views of third- 3 party governance. 4 The purpose of the workshop is to provide an 5 opportunity in a public forum for FDA to hear from 6 those with experience and an informed view on this 7 issue. Therefore, several FDA representatives are 8 in attendance and we listen closely to the 9 perspectives described over the next two days. 10 We'll also be opening a public docket soon on this 11 topic, which will provide an opportunity for 12 additional comment from interested parties to be 13 entered into the public record. 14 The workshop and the opening of the public 15 docket for comment are just the initial steps that 16 FDA is taking as we begin to explore the concept of 17 third-party governance and learn about some of the 18 governance models that have been or are being used 19 in other sectors. 20 The workshop will be moderated by Abby 21 Dilley from RESOLVE, and I'll now turn the 22 microphone over to her. Thanks, Abby.</p>	<p style="text-align: right;">Page 11</p> <p>1 comment period tomorrow, where people have 2 preregistered per the notice about this meeting to 3 speak during that period. 4 We also have people not only participating 5 in the room, but also virtually. There is a 6 webcast going now. There's an e-mail address. For 7 those of you who are listening remotely, the way to 8 access that e-mail to send a question is through 9 just a click right on the website. 10 So if you've gotten into the meeting, then 11 you're on the website. You just need to click on 12 that. So we'll be, at periods of time, taking some 13 of those questions that we're receiving remotely to 14 try and, again, expand the opportunity to gather 15 information and from different people 16 participating, both in person and remotely. 17 Part of helping support a meeting is to keep 18 the meeting on time, on task, and on track. So 19 hopefully, we'll be able to do that, and then also 20 establish some meeting protocols to help support 21 the meeting. 22 I have worked on tobacco control and</p>
<p style="text-align: right;">Page 10</p> <p>1 Workshop Moderator – Abby Dilley 2 MS. DILLEY: Good morning. So as David 3 said, my name is Abby Dilley, and the organization 4 I work for is named RESOLVE. It may be an 5 unfortunate name, given what Mitch said. We're not 6 resolving issues today. It is for primarily 7 information gathering from diverse perspectives. 8 And my role will be as a moderator, and in that 9 capacity to help support -- along with Beth Weaver, 10 my colleague, and others at CTP, some staff from 11 CTP, to hopefully support a good couple-a-day 12 meetings to achieve that particular goal, which is 13 to gather information. 14 We're doing that in a variety of ways. 15 We'll have presentations from a variety of invited 16 speakers both today and tomorrow. And then we'll 17 also have question and answer sessions, some 18 immediately after the presenters give their remarks 19 so we have questions for clarification; and then we 20 also, as you see over the course of the agenda for 21 the day and a half -- that there is opportunity for 22 longer stretches of Q&A; and then also a public</p>	<p style="text-align: right;">Page 12</p> <p>1 regulation issues for a while, but I don't pretend 2 to be an expert on this particular issue. Some of 3 my questions that I may ask in follow-up might 4 reflect that limited expertise, but hopefully they 5 won't be too out there. 6 I will read a question submitted either via 7 e-mail or we have cards over on the table over 8 there, if people would prefer to submit questions 9 via card. There are cards there. You can just put 10 them in the basket, and over lunch break, for 11 example, we can gather some more information and 12 questions from the website, the e-mail address, and 13 also cards. And there may be need for follow-up to 14 make sure that I express the question correctly. 15 So I just want to give people a sense of how 16 we're gathering information and have an opportunity 17 to put in some questions to the panel members. 18 I just wanted to walk through the agenda. 19 Hopefully, when you came in and got your name tag, 20 you also received some materials, including the 21 agenda for today, and that looks like this with 22 that on there. And there are two stapled pieces</p>

<p style="text-align: right;">Page 13</p> <p>1 that are the slides, the speakers. I think they're 2 today and tomorrow. No, just today. Sorry, just 3 today. And then there is a feedback form in blue. 4 And when you have a chance to fill that out, 5 there's a place over here on the table, again, for 6 those forms.</p> <p>7 So I just wanted you to know that those 8 materials are there. If you haven't gotten them, 9 they're out at the front desk where you walked in 10 to get your name tag.</p> <p>11 If you look at the agenda, there are 12 basically five primary sections on the agenda. 13 There's first an overview of the IOM report, and 14 MRTPs, and governance structures. And Daniel 15 Carpenter is here to give that overview. We'll 16 then take some questions and answers after his 17 presentation.</p> <p>18 Then we have a panel that will go 19 over -- through a break as well, a panel of public 20 health experts, some of whom have written articles 21 on this topic as well as researchers and the 22 academic and other communities conducting research</p>	<p style="text-align: right;">Page 15</p> <p>1 the beginning of the day.</p> <p>2 Then the last section of the meeting will be 3 a panel of representatives from companies, tobacco 4 manufacturers, and other products, as well as 5 research and policy consultants, some of whom have 6 developed ideas around third-party governance 7 structures.</p> <p>8 So that's the five sections, if you will, of 9 the overall agenda.</p> <p>10 Now, for the format for presentations and 11 Q&A, each speaker has been given some time, about 12 10, 15, in some circumstances, like our first 13 presenter, 20 minutes to give comments. And then 14 we'll have an opportunity -- there will be some 15 lights up here to give you the sign of, you're 16 getting close to the end of your time, and then 17 red. Just try and keep relatively within the time 18 limits.</p> <p>19 Then we'll have some opportunity to ask some 20 follow-up questions for clarification. We'd really 21 like to keep those as much as possible to 22 clarification questions from the presentation, so</p>
<p style="text-align: right;">Page 14</p> <p>1 in this area or relevant areas.</p> <p>2 As you can see from the overview of the 3 agenda, the Q&A period for that session will be 4 after lunch. And just on that note, we're taking 5 an hour break for lunch. And outside, you'll see a 6 book -- if you're not familiar with this area, 7 there's a book of suggestions for nearby areas so 8 you can have lunch and be back here in time for the 9 start-up of the Q&A session for that first panel.</p> <p>10 Then the third section is a panel of experts 11 with experience developing and are involved with 12 third-party governance models. Just a note on 13 that, in the IOM report -- and I'm sure Daniel will 14 speak to this, some of the models suggested in 15 there. This is to have a couple other models to 16 throw into the mix for consideration and think 17 through in terms of how they approached third-party 18 governance structures. And then there will be an 19 opportunity for additional Q&A after that.</p> <p>20 Then tomorrow morning, we will start with a 21 public comment period. That's really the fourth 22 section in the agenda, if you will, tomorrow, at</p>	<p style="text-align: right;">Page 16</p> <p>1 we're extracting as much information out of those, 2 and then keep more of the substantive questions for 3 the panels to the Q&A.</p> <p>4 Obviously, that's hard to distinguish very 5 discretely between those two, but mostly, it's to 6 make sure we stay on time and then can get to the 7 longer Q&A period with more detailed questions.</p> <p>8 We will have people who have microphones. 9 This is being recorded, so there's a transcript 10 that will ultimately be available from the CTP 11 website. So we want to use the microphones, both 12 so people can hear the question -- it's a big room; 13 you can hear fairly well now, but I'm also on a 14 mic -- so everybody can hear the question and keep 15 things moving along as well as being able to be 16 part of the transcript.</p> <p>17 If you would, introduce yourself. We're not 18 going to go around the room and have everybody 19 introduce themselves, but if you could do that in 20 asking a question, that would be great. If you 21 fill out a card or people are sending a question by 22 internet, you don't need to identify yourself.</p>

<p style="text-align: right;">Page 17</p> <p>1 We're not going to necessarily list those, but just 2 take questions as we go. But I think, just in the 3 room, it's helpful, a little bit helpful. 4 Then at the conclusion of each panel, those 5 sections, except for the public comment period 6 because we don't have Q&A associated with public 7 comment, there will be the opportunity, at least, I 8 think, for almost every session, at least an hour 9 for questions for the panel members. So there will 10 be opportunity to do that. 11 Again, sometimes it will be from holding up 12 hands. Sometimes, it will be from taking questions 13 off the e-mails and from the basket over there, 14 where you can put some index-card questions. And 15 we may not get to every question. 16 We'll try and get to as many as we can 17 within the allotted time. We really don't want to 18 run off schedule, so we'll keep that within the 19 context of the Q&A. But if you did submit a 20 question or we didn't get to your question when you 21 raised your hand, just put it in the basket, and it 22 will be part of the materials that are all in the</p>	<p style="text-align: right;">Page 19</p> <p>1 is, that you provide your perspectives and 2 opinions. And we can do it in a respectful manner. 3 The other thing I would just say, just in 4 terms of helping support, able to hear, is to turn 5 off your cell phones. Or if you haven't already 6 done that, if you could put it on vibrate or 7 something, we don't have musical accompaniment over 8 the course of the day. And then if you also have 9 questions or want to talk to your neighbor, if you 10 could go outside and do that, that would be 11 appreciated, so people can hear the presenters and 12 the questions. 13 I know they haven't sat in their press 14 seats, but if there is media, please, if you want 15 to have any interviews with any of the CTP staff, 16 you need to go through Raquel Ortiz. 17 Is she here? I don't see her. There she 18 is. You're standing up, and I still missed you. 19 Sorry. 20 You can talk to Raquel back there to 21 schedule. For others, if there are media, again, 22 in the room, and I don't know if there are, take</p>
<p style="text-align: right;">Page 18</p> <p>1 spirit of trying to collect as much information and 2 input as possible, and same with the e-mails. 3 Just a couple more things, then we'll get 4 started. Just in terms of the meeting protocols, 5 again, to help support the goals of the meeting, to 6 try and gather as much information as possible; to 7 stay on topic; to be brief with your questions. 8 I have been in meetings where people have 9 said I have five questions with three subparts for 10 each question. And then you really take up a lot 11 of time. So it'd be great to try to limit the 12 questions that you think are most important for 13 you, and then to be brief in asking questions so we 14 can take as many as possible. And then finally, 15 just as part of that, to be respectful of 16 everyone's time. 17 Everyone came, an invitation. We're trying 18 to get to hear from all of you as much as possible. 19 And we can express opinions and perspectives in a 20 respectful manner. As Mitch said, there are very 21 strong feelings around this topic, in this area 22 generally, and certainly that's what the request</p>	<p style="text-align: right;">Page 20</p> <p>1 any conversations with other non-CTP folks outside 2 the room. We would appreciate that, again, to 3 minimize noise. 4 Lastly, I would just say I think I mentioned 5 that there will be a transcript. There will also 6 be a docket established soon. So if there are 7 additional follow-up comments from this, or you 8 thought of something getting back to your offices, 9 or on your way, check the CTP website periodically, 10 and the transcript will be up there at some point, 11 and then also a docket to provide additional 12 comment. 13 So with that, we've gone through the 14 preliminaries of the flow of the meeting and 15 everything else. 16 Did I miss anything? Okay. 17 So with that, we will turn to our first 18 presenter this morning, Dr. Daniel Carpenter, who 19 is the Freed Professor of Government at the 20 Department of Government at Harvard University and 21 a member of the IOM committee. So I'll have you 22 come up and we'll get started.</p>

<p style="text-align: right;">Page 21</p> <p>1 Presentation – Daniel Carpenter</p> <p>2 DR. CARPENTER: Thanks, everybody, for</p> <p>3 coming out today. Let me begin. I'm Dan</p> <p>4 Carpenter. I want to begin with a couple of very</p> <p>5 important caveats. First off, while I was a member</p> <p>6 of the IOM committee on scientific standards for</p> <p>7 studies on modified-risk tobacco products, I cannot</p> <p>8 today speak officially for that committee. The</p> <p>9 voice of that committee is the report.</p> <p>10 So if there is anything that I say that</p> <p>11 differs from the very large report that is</p> <p>12 available in PDF form and is printed, you should</p> <p>13 trust the report and not me. Okay?</p> <p>14 It also goes without saying that I cannot</p> <p>15 speak today and that the views that I am expressing</p> <p>16 don't represent necessarily those of the committee.</p> <p>17 I'm going to try to summarize some of our</p> <p>18 deliberations. And of course, I'll quote from our</p> <p>19 report in relevant statute.</p> <p>20 What I'm saying today is not necessarily the</p> <p>21 judgments or the opinion of the Institute of</p> <p>22 Medicine, separate from the committee, and it</p>	<p style="text-align: right;">Page 23</p> <p>1 degree of external validity greater than is often</p> <p>2 seen in the kinds of protocols of studies that we</p> <p>3 see for drugs and devices -- will first off reduce</p> <p>4 industry tobacco harm. But second -- and I think</p> <p>5 here's the really distinguishing key feature, and,</p> <p>6 again, apologies if you already know</p> <p>7 this -- benefit the health of the population as a</p> <p>8 whole, taking into account those who would be</p> <p>9 likely to use tobacco products and those who would</p> <p>10 not.</p> <p>11 It's that public health standard that</p> <p>12 distinguishes many of these approval decisions.</p> <p>13 You can make the analogy, again, to drug and</p> <p>14 devices. This is, if you will, individual efficacy</p> <p>15 and safety, which you see in the drug and device</p> <p>16 world, but this is not in the drug and device</p> <p>17 world. We don't consider these kinds of spillover</p> <p>18 effects, if you will.</p> <p>19 The other aspect of the statutory foundation</p> <p>20 is that Congress explicitly gives the FDA authority</p> <p>21 to regulate the preparation and conduct of the</p> <p>22 studies issued in support of an MRTP application.</p>
<p style="text-align: right;">Page 22</p> <p>1 certainly isn't the judgment of Harvard University.</p> <p>2 They've been checking my e-mails to make sure.</p> <p>3 (Laughter.)</p> <p>4 DR. CARPENTER: Anybody get that joke?</p> <p>5 I have done some work in some of this area,</p> <p>6 funded by a number of related foundations; again,</p> <p>7 the usual caveat I am going to apply.</p> <p>8 So the statutory foundation that I think</p> <p>9 we're all familiar with here is in Section 911 of</p> <p>10 the Family Smoking Prevention and Tobacco Control</p> <p>11 Act. And that section applies to modified-risk</p> <p>12 tobacco products, essentially, the drug and device</p> <p>13 approval model that we've seen elsewhere. Not</p> <p>14 exactly. I want to be clear, this is an analogy.</p> <p>15 Okay? But the idea is that there's pre-market</p> <p>16 approval for these products. And the health</p> <p>17 effects have to be demonstrated a priori.</p> <p>18 So the relevant controlling language comes</p> <p>19 from 911(g), that the secretary can allow these to</p> <p>20 be commercially marketed if and only if the</p> <p>21 applicant has demonstrated that such product, as it</p> <p>22 is actually used by consumers -- which involves a</p>	<p style="text-align: right;">Page 24</p> <p>1 This also has a rich history, going back to the</p> <p>2 1938 Food, Drug, and Cosmetic Act, the 1963</p> <p>3 investigational new drug rules, the statutes that</p> <p>4 enabled those, the Kefauver Harris amendments, and</p> <p>5 so forth. So there's a long legal history here.</p> <p>6 I think this is key. The committee on which</p> <p>7 I served was basically authorized in the statute.</p> <p>8 There are a lot of IOM committees that meet on a</p> <p>9 lot of things, including tobacco issues and other</p> <p>10 things. Many of them are called by the FDA without</p> <p>11 prior congressional authorization.</p> <p>12 Part of the charge of this committee was to</p> <p>13 respond to the FDA, but part of the charge of this</p> <p>14 committee was in fact to engage in a consultation,</p> <p>15 which was required by statute, which was required</p> <p>16 by us. And just to read here, "The consultation is</p> <p>17 required in statute and it allows the FDA to issue</p> <p>18 regulations or guidance. But they shall be</p> <p>19 developed in consultation with the IOM, with the</p> <p>20 input of other appropriate scientific and medical</p> <p>21 experts on the design and conduct of such studies</p> <p>22 and surveillance." Those two terms, I think, are</p>

<p style="text-align: right;">Page 25</p> <p>1 going to be very important as we move forward.</p> <p>2 So what happened? Well, again, you all know</p> <p>3 this. The relevant recommendation is in the list</p> <p>4 of recommendations at the end of the report. And</p> <p>5 there is a lot of time that we could spend</p> <p>6 unpacking the language here, but I just want to</p> <p>7 alert your attention to a couple of quick facts.</p> <p>8 So here's the recommendation as it reads in</p> <p>9 the published report. MRTP sponsors should</p> <p>10 consider use of independent third parties to</p> <p>11 undertake one or more key functions, including the</p> <p>12 design and conduct of research, the oversight of</p> <p>13 specific studies, and the distribution of sponsor</p> <p>14 funds for research.</p> <p>15 Such independent third parties -- and I'm</p> <p>16 going to put my own parenthesis here -- if they are</p> <p>17 used -- should be approved by the FDA in advance of</p> <p>18 the research.</p> <p>19 So a couple of points on this. First off,</p> <p>20 IOM recommendations are usually their</p> <p>21 recommendations. Right? They're not binding</p> <p>22 guidance. We can't make the rules. We don't have</p>	<p style="text-align: right;">Page 27</p> <p>1 essentially the mechanism by which drug and device</p> <p>2 approval in R&D in the United States works. That's</p> <p>3 what's going on here. Probably a wise thing, if</p> <p>4 you want a third party that has credibility, to</p> <p>5 make sure that the person reviewing your</p> <p>6 application as an MRTP sponsor views it as</p> <p>7 independent and credible.</p> <p>8 Second, the FDA is probably going to have a</p> <p>9 view about what is best -- supposed to have a view</p> <p>10 about what is best not only for the MRTP sponsor,</p> <p>11 but also for the public health at large. That's</p> <p>12 one of its charges under this law. And so it's</p> <p>13 going to be using, in theory, different criteria</p> <p>14 and perhaps more appropriate criteria for the</p> <p>15 selection of independent third parties.</p> <p>16 It doesn't mean and we did not say -- we</p> <p>17 discussed this -- that the FDA should a priori name</p> <p>18 the third parties. Our recommendation was simply</p> <p>19 that there may be multiple candidates for a third</p> <p>20 party, and there are a number of ideas about what</p> <p>21 this could include, and that the FDA might reject</p> <p>22 some of those and suggest that some of those are</p>
<p style="text-align: right;">Page 26</p> <p>1 the legal authority to make rules. No committee</p> <p>2 does for the FDA.</p> <p>3 So there are two recommendations here. One</p> <p>4 is that the MRTPs sponsors should consider using</p> <p>5 these third parties; and, second, that perhaps not</p> <p>6 every aspect of the research, but some should be</p> <p>7 managed by or undertaken by these third parties,</p> <p>8 including design and conduct of research -- that's,</p> <p>9 by the way, explicitly an echo of the statutory</p> <p>10 language -- oversight of specific studies, that</p> <p>11 would fall under design and conduct; distribution</p> <p>12 of sponsor funds for research. That would also</p> <p>13 fall under design and conduct.</p> <p>14 Such independent third parties should then</p> <p>15 be approved by the FDA in advance of the research.</p> <p>16 Why did we suggest that? A couple of reasons.</p> <p>17 Number one, the FDA is going to be the one</p> <p>18 ultimately judging these claims. It's the</p> <p>19 ultimate -- as I've argued in my book, Reputation</p> <p>20 and Power, in the pharmaceutical realm, the</p> <p>21 ultimate veto player over entry into the market.</p> <p>22 And that's a brute way of describing it, but that's</p>	<p style="text-align: right;">Page 28</p> <p>1 not appropriate, and might suggest that others are</p> <p>2 more appropriate.</p> <p>3 So it's important to understand that -- and</p> <p>4 here I can summarize a few of the deliberations,</p> <p>5 but, again, to the extent I can't speak for the</p> <p>6 committee -- when this committee met, the question</p> <p>7 of governance and how studies would be organized,</p> <p>8 conducted, funded was very much on our minds.</p> <p>9 However, the idea of what you would call, say,</p> <p>10 third-party governance, was a little bit less so,</p> <p>11 not so much that we thought it was inappropriate or</p> <p>12 more appropriate. We just had a very open mind.</p> <p>13 Some of the very first suggestions for the</p> <p>14 idea that some of this research should not be</p> <p>15 conducted and, in fact, would not be conducted in</p> <p>16 support of MRTP applications from tobacco companies</p> <p>17 came, in fact, from representatives of some tobacco</p> <p>18 company units at the second meeting of the IOM</p> <p>19 committee, which was the first public meeting.</p> <p>20 In particular, Lars Erik-Rutqvist</p> <p>21 mentioned -- and I'm paraphrasing -- at one</p> <p>22 particular meeting here that, look, there are a</p>

<p style="text-align: right;">Page 29</p> <p>1 wide variety of potential users of these MRTP 2 products, including adolescents, and tobacco 3 companies cannot and should not conduct research on 4 those populations. We would need to find somebody 5 else to do that.</p> <p>6 A number of other people echoed a similar 7 sentiment. Now, I'm paraphrasing that, but this 8 letter, which I'm quoting to you is available as an 9 appendix to the IOM report. So if I've 10 mischaracterized anything that Mr. Rutqvist has 11 said -- and I'm not sure if he's in the room 12 here -- in my words, just read the letter.</p> <p>13 Essentially, what he said were two things. 14 First, some of this research just won't end up 15 being done by companies, particularly when there 16 are at-risk populations being done. Second, the 17 infrastructure that eventually issues in support of 18 MRTP research must promote public trust and 19 research in MRTPs.</p> <p>20 There was widespread consensus at the 21 meeting, which I will explain later, that that kind 22 of public trust, not just -- I'm talking about</p>	<p style="text-align: right;">Page 31</p> <p>1 lead when studying sensitive subpopulations such as 2 adolescents," merely a contributor and not the 3 lead, always, when studying sensitive 4 subpopulations such as adolescents.</p> <p>5 "As the committee prepares its report --" 6 and this, by the way, was sent in August 2012 or 7 '11, excuse me, before the report was issued -- "I 8 hope you will consider the importance of addressing 9 the need for FDA, with support from other 10 stakeholders, to establish an infrastructure that 11 allows for collaborative research, which includes 12 financial and scientific contributions from the 13 industry.</p> <p>14 "Again, this is particularly important when 15 conducting research on sensitive subpopulations 16 such as adolescents, the type of research industry 17 will not conduct on its own" -- not "should not," 18 not "may not," "will not." This is his 19 statement -- "due to ethical and product 20 stewardship concerns.</p> <p>21 "There are examples of government industry 22 collaboration to draw upon. And he notes one that</p>
<p style="text-align: right;">Page 30</p> <p>1 public opinion. I'm talking about trust in the 2 scientific community, the credibility of research 3 is right now, especially compared to the drug, and 4 device, and other world, lacking in the area of 5 tobacco products, including modified-risk tobacco 6 products.</p> <p>7 To go further, in part because of this 8 letter and these discussions, this letter is both 9 important in its own right and evocative of some 10 very important discussions -- again, it's an 11 appendix to the IOM report -- this is Rutqvist, "We 12 hope that the implementation of the Tobacco Control 13 Act will ultimately lead to the establishment of a 14 more trusting environment," -- again, implicitly, 15 one that does not exist now -- "in which 16 stakeholders can share information and perhaps even 17 collaborate on research initiatives.</p> <p>18 "We can foresee a time when our scientists 19 and marketing professionals work closely with 20 government and academia in research that is of 21 national, global significance. However, industry 22 should always be merely a contributor and not the</p>	<p style="text-align: right;">Page 32</p> <p>1 we also discuss at length in the report, the Health 2 Effects Institute, an independent research 3 organization that provides high-quality, impartial, 4 and relevant science on the health effects of air 5 pollution.</p> <p>6 "HEI receives half of its core funds from 7 the EPA, half from the worldwide motor vehicle 8 industry. Since I realize the time has not yet 9 come for the tobacco community to support an HEI- 10 like approach, I certainly think that it or some 11 other collaborative approach is a goal we should 12 strive for."</p> <p>13 So here's a problem. Rutqvist's letter 14 refers in part to research on adolescent 15 populations. The problem is, of course, that every 16 MRTP product is potentially consumable, indeed 17 likely consumable sooner or later by one or more 18 adolescents. One or more, I think, is the 19 understatement of the year.</p> <p>20 Second, the law requires approval based upon 21 a public health standard. It requires approval 22 considering what are the effects of the product</p>

<p style="text-align: right;">Page 33</p> <p>1 going to be on those who consume products now, 2 tobacco products now, and those who do not. 3 In other words, at some level, every product 4 is going to have to undergo research on sensitive 5 subpopulations such as adolescents, maybe not 6 adolescents in every single case, but every product 7 is liable -- I don't mean that in the legal sense, 8 but eligible to be subject to research, rigorous 9 studies on sensitive populations. 10 So this is a much broader point, a much 11 broader application -- and this was also the 12 committee's thinking -- than simply whether or not 13 adolescents were being studied. 14 Let me advance some further concerns here. 15 So let me just summarize what I think was 16 the consensus of the committee. And, again, I want 17 to emphasize that in the points I'm about to give 18 you, I'm speaking for myself here. I can't speak 19 for the committee, but I can refer you to points in 20 the report, which basically substantiate what I'm 21 about to say. 22 Right now, industry-sponsored research on</p>	<p style="text-align: right;">Page 35</p> <p>1 of this issue. This is not a statement about blame 2 about who's to be responsible for this. It's a 3 statement about where we are. This is where we 4 are. These are the facts. This is an empirical 5 statement of the status quo. 6 Second, following from number one, the most 7 credible institutions in science and research, 8 including my own university and multiple schools, 9 simply won't accept research funding from tobacco 10 industry sponsors to conduct most trials. There 11 may be in some cases, some particular cases where 12 that has been, but as a general policy, most 13 credible institutions simply will not, which brings 14 us to a problem. 15 Under the status quo -- and this is 16 something we worried about greatly as a 17 committee -- it's possible that, if you don't have 18 credible research and those health claims are not 19 demonstrated, you don't have a market here, which 20 is to say, you don't have products that ever appear 21 before the FDA, because the FDA must consider these 22 health properties of MRTPs to be credibly</p>
<p style="text-align: right;">Page 34</p> <p>1 tobacco products is not trusted. I'm not saying 2 it's not trusted at all. It's just not trusted 3 with near the kind of scientific credibility that 4 one sees in devices, drugs, or a wide variety of 5 other medical research. 6 Two points here. First, that's a finding, 7 not a recommendation, a finding, number 10 of the 8 IOM report, from a wide variety of scientists who 9 are far better qualified than I am as an individual 10 to weigh in on that point; some of them actually 11 from the pharmaceutical industry, top-notch cancer 12 researchers, top-notch OTI researchers, a range of 13 folks. 14 If you're looking for an example of where 15 that residue of distrust comes from, I would refer 16 to my colleague, Allan Brandt's award-winning book, 17 Cigarette Century. 18 I mean this as a statement of facts, not as 19 a statement of blame. I know, going into this, 20 although I haven't been working on this theme of 21 research quite so intensively of late, that there 22 are some passionate convictions on multiple sides</p>	<p style="text-align: right;">Page 36</p> <p>1 demonstrated. That's science. And if the research 2 is not credible, it's not a matter of, well, maybe 3 the FDA shouldn't approve them; the FDA can't. 4 There are definite scientific standards here. 5 That's the same thing, by the way, the same law, 6 which we've had for 50 to 60 years in the area of 7 drugs and devices; that there is a scientific bar 8 which has to be passed. 9 So to go back, what was the recommendation? 10 Just to sort of unpack it a little bit. Again, the 11 IOM did not consider -- the committee did not 12 consider itself in a position to dictate to 13 sponsors; and, of course, all of its 14 recommendations are precisely that, their 15 recommendations. So we don't make rules. 16 The MRTP sponsors should consider the use of 17 independent third parties to undertake one or more 18 key functions. It doesn't necessarily mean that 19 all functions of a study or a research program 20 would be undertaken by such third parties. 21 If they're done, if third parties are used, 22 when they're used, they're going to be more</p>

<p style="text-align: right;">Page 37</p> <p>1 credible and they're going to meet the goals of 2 public health more when they are approved by 3 the -- I just hit the wrong button, so let's go 4 here. 5 When such independent third parties -- or 6 when the independent third parties are called into 7 action, into consultation, into use, the FDA is the 8 appropriate body from which sanction could issue 9 for the use of these parties. That doesn't 10 necessarily mean legal sanction. It just says, 11 basically, the FDA can give advice on, we think 12 this is an independent third party, high-quality 13 research. By the way, the FDA has done that in 14 drugs and devices for 60 years. There's a long- 15 established administrative legal precedent for the 16 FDA deciding which scientific units are credible 17 and which scientific units are not. Read chapter 4 18 of my book, Reputation and Power. 19 So here are some possibilities. I think the 20 first one is the most relevant. It's the Health 21 Effects Institute, and it was created -- not unlike 22 the times we're in now -- in the context of severe</p>	<p style="text-align: right;">Page 39</p> <p>1 to it, but there's some big differences here. 2 Number one, it was also created to advance 3 research in the context of uncertainty. But it's 4 clearly not independent, and, in fact, it's 5 regulated by Congress with a wide variety of sort 6 of positions on its board that are kind of -- it's 7 kind of like the old European corporatist model. 8 You know, you've got one from the socialists, one 9 from the Greens, one from the business and 10 everything like that. That's kind of the 11 Reagan-Udall model. 12 It's also not nearly as old or as widely 13 respected -- I think that's fair to say -- as is 14 the Health Effects Institute in terms of the 15 legacy, the scientific legacy that it has. That's 16 not to say I think it's disrespected. It just 17 doesn't simply have the benefit and the 18 legitimization of accumulated time and experience 19 yet. 20 So a couple of additional points and then I 21 can talk a little bit about the special rule, which 22 I know would be of interest, but I can also just</p>
<p style="text-align: right;">Page 38</p> <p>1 distrust, even ideological distrust, of industry 2 research, and on the part of industry, distrust of 3 the EPA. 4 The idea was, okay, let's have both parties 5 put money into an institute, which doesn't 6 necessarily, by the way -- the HEI doesn't 7 necessarily conduct all the research on its own. 8 It often acts as kind of like NIH review panels for 9 deciding where money should be allocated. It's as 10 much a granting agency as a research university. A 11 lot of universities and research institutes are 12 like that. 13 It is praised by Rutqvist as a possibility, 14 and it's praised by many others as a possibility. 15 So Rutqvist in his letter specifically mentions the 16 Health Effects Institute as a model that not 17 necessarily should be slapped willy-nilly without 18 thought on this area, but should be considered. 19 The Reagan-Udall Institute is also mentioned 20 in the report. I'm going to give you, again, my 21 own gloss on this. I think this is somewhat less 22 relevant. It's a possibility. I'm certainly open</p>	<p style="text-align: right;">Page 40</p> <p>1 conclude. 2 I want to emphasize two kind of general 3 points. The first is, I know there's been some 4 concern that, why was the IOM recommending this? I 5 mean, this is about how research is organized. 6 This is not about, say, what sort of statistical 7 test to use, what sort of animal models to use, and 8 things like that. 9 Again, I refer you back to the statute, the 10 design and conduct of scientific studies and 11 surveillance. Conduct clearly includes the 12 organization, the institutional arrangement of 13 research. It has been understood that way in 14 federal law, in federal regulatory practice at the 15 FDA for more than a half-century. 16 If Congress, in fact, could not and the FDA 17 could not govern the conduct of research, there 18 would be no basis for any law, regulation, or 19 guidance -- and by the way, there are dozens of 20 these sorts of guidances -- from the public health 21 service and a range of others to govern IRBs, and 22 the way they meet and conduct things, their</p>

<p style="text-align: right;">Page 41</p> <p>1 business.</p> <p>2 Second, we have to understand sooner or</p> <p>3 later that regulation constitutes marketplaces. It</p> <p>4 doesn't necessarily just intervene into a</p> <p>5 marketplace. It reconstitutes them. And if the</p> <p>6 MRTP market is to succeed in generating public</p> <p>7 health objectives, especially in the long run, it</p> <p>8 has to be trusted, trusted by the public, trusted</p> <p>9 by the scientific community, trusted by physicians,</p> <p>10 trusted by public health experts, for that matter,</p> <p>11 at some level, trusted by investors.</p> <p>12 If the research is not trusted -- and this</p> <p>13 is where I am going to give you my own view, and</p> <p>14 I'm not saying this is inconsistent with the IOM;</p> <p>15 I'm just again not going to paste Harvard or the</p> <p>16 IOM on these; I'm just going to emphasize my own</p> <p>17 view -- good scientific collaboration will</p> <p>18 languish. There is that possibility. Rutqvist's</p> <p>19 letter points to it, again.</p> <p>20 Second, products will not be developed</p> <p>21 rigorously in the way that they often are for</p> <p>22 medical devices and pharmaceuticals. Applications</p>	<p style="text-align: right;">Page 43</p> <p>1 extensive debate on the issue and wound up</p> <p>2 allowing, for example, UCLA to accept tobacco</p> <p>3 funding.</p> <p>4 So did you really mean that there's a</p> <p>5 ranking of institutions and the most credible ones</p> <p>6 don't accept, or did you mean most of the credible</p> <p>7 ones don't accept?</p> <p>8 DR. CARPENTER: I want to be a little</p> <p>9 careful here because we're talking a little bit</p> <p>10 about academic status hierarchies, and I'm from</p> <p>11 Harvard, which tends to place --</p> <p>12 MR. ROSE: The Duke of the North.</p> <p>13 (Laughter.)</p> <p>14 DR. CARPENTER: Yes. Exactly.</p> <p>15 First off, I didn't -- I mean, this is a</p> <p>16 generalization and, as I said, there are certain</p> <p>17 cases -- as I said during the talk, there are</p> <p>18 certain cases when universities have allowed for</p> <p>19 those exceptions.</p> <p>20 The very debate that occurred in the</p> <p>21 California case, by the way -- and I think,</p> <p>22 actually, UVA, by the way, is looking at this, too,</p>
<p style="text-align: right;">Page 42</p> <p>1 will not be accepted. The FDA simply won't have</p> <p>2 the scientific basis or legal basis with which to</p> <p>3 accept them. And healthy efficient markets, based</p> <p>4 on information with which people can make sound,</p> <p>5 informed choices between products and conduct, if</p> <p>6 you will, optimization, explicit or implicit, among</p> <p>7 available choices to them will not take hold.</p> <p>8 Let me conclude there. If people want, I</p> <p>9 can talk about the special rule and some of the</p> <p>10 things that I read there, but I'll just -- thank</p> <p>11 you very much.</p> <p>12 (Applause.)</p> <p>13 MS. DILLEY: Thank you very much. So we'll</p> <p>14 now take some questions for Daniel.</p> <p>15 MR. ROSE: Yes. Hi. Jed Rose. I'm a</p> <p>16 professor at Duke University. And I just had a</p> <p>17 question about one of the statements that you</p> <p>18 listed almost as a finding, "The most credible</p> <p>19 institutions do not accept tobacco industry</p> <p>20 funding." And two exceptions that come to mind</p> <p>21 are -- well, one, Duke University; and, second, the</p> <p>22 University of California system, which had a very</p>	<p style="text-align: right;">Page 44</p> <p>1 so it's not just the two you mentioned.</p> <p>2 But the very debate that occurred in the</p> <p>3 California case points, I think, to the level of</p> <p>4 distrust and felt need for internal regulation that</p> <p>5 the University of California system felt that it</p> <p>6 was needed.</p> <p>7 I should point out here that what we do want</p> <p>8 to avoid -- let me just speak for myself -- is a</p> <p>9 world where we just have a least-common</p> <p>10 denominator. So there's one university out there</p> <p>11 that is willing to accept tobacco money, and nobody</p> <p>12 else is, and all of the MRTP funding and research</p> <p>13 that is in support of 911 applications goes through</p> <p>14 that university or, say, to.</p> <p>15 I would not consider that a very credible or</p> <p>16 rigorous system of scientific organization or of</p> <p>17 preparation of MRTP applications, no matter what</p> <p>18 the ranking of those individual universities.</p> <p>19 MR. ROSE: Even Harvard?</p> <p>20 DR. CARPENTER: Yes, even Harvard. If the</p> <p>21 only one were Harvard -- and by the way, Harvard</p> <p>22 had a long history of accepting tobacco industry</p>

<p style="text-align: right;">Page 45</p> <p>1 money for research, so it's not to say that -- you 2 know, I'm not trying to -- this is a holier-than- 3 thou, or we don't do this and everybody else does. 4 I'm talking about a very general status quo. 5 MS. DILLEY: Other questions for Daniel? 6 We'll get to you. It's not an easy room to 7 navigate. Go ahead and introduce yourself. 8 MR. DILLARD: Jim Dillard, Altria Client 9 Services. I was curious about the conversation 10 that you guys might have had, particularly on the 11 governance. Given medical device -- and you 12 alluded to medical device and pharmaceuticals 13 both -- having a lot of history working with the 14 FDA, and the FDA really being the governance 15 structure, what was your conversation between 16 confidence in FDA to be able to pull this off 17 versus the necessity for another third party, who 18 would be really an intermediary between the 19 research that might be funded by the industry and 20 the FDA's ability to be able to act as that 21 governance structure? 22 DR. CARPENTER: Yes. That's a good</p>	<p style="text-align: right;">Page 47</p> <p>1 a bunch of applications come in: Duke, University 2 of California, Harvard. And that entity, HEI, and 3 not the company, decides who gets the contract. 4 So the idea -- and this is the HEI idea, and 5 I'm just floating this as a possibility; it's not 6 something we said this must happen. But that idea 7 removes the potentiality of an implicit quid pro 8 quo between the company and the potentially 9 repeated recipient of contract research funds. 10 Keep in mind, too -- and I think this is a 11 real key part about NIH review panels, which I'm 12 just throwing out there for a case of 13 example -- they rotate. So it's not the same 14 people again, and again, and again that a certain 15 university or provost at a high-ranking medical 16 center gets to kiss up to. I'm speaking a little 17 bit casually here. But there have been concerns 18 about exactly that kind of thing. 19 So by the rotation at some level, you try to 20 ensure that there's a fresh panel each time, which 21 makes these judgments about where the funds should 22 go, and then what the design of the studies should</p>
<p style="text-align: right;">Page 46</p> <p>1 question, and I am interpreting it as somewhat 2 open-ended. Let me try to sort of scratch my 3 neurons here a little bit and remember. So I do 4 remember that, in the discussion about the kind of 5 institutions that one might see under this rule. 6 And I really want to emphasize that it's, at some 7 level, open ended, and that is not to say 8 infinitely open ended. But there's room for 9 discretion here on the part of the FDA and on the 10 part of MRTTP sponsors, as I'm viewing it, as a 11 committee member. 12 The kind of arrangement would not be that a 13 third-party structure would govern the research so 14 much. If you look at the HEI, essentially, you put 15 money into a pool, into which by the way the 16 government also puts money. And I'm not saying 17 that that's necessarily what we need to do here. 18 But they put that money into a pool, and 19 then you assemble something like -- think about an 20 NIH review panel. It's a bunch of people who are 21 just demonstrably independent of the sponsor. And 22 they say, "Who's going to work on this study?" And</p>	<p style="text-align: right;">Page 48</p> <p>1 be. 2 Now, part of your question I think also gets 3 at governance, which is to say governance -- it 4 gets at a number of things. It gets at governance 5 in the sense of what's the organization? What's 6 the funding? It gets at governance in the sense of 7 the nitty-gritty of research design. 8 We had a lot of discussions about this 9 question about adolescence and other sensitive 10 populations. And that was another case in which we 11 felt that, if there were proposals from research 12 units -- again, universities and others -- coming 13 into this third-party entity, which had this 14 TR -- what's the acronym that everybody's using 15 now? 16 No, not MRTD. TRGE, tobacco research 17 governance entity; so like the HEI; that they would 18 say, well, look, we think this design, this study 19 design, crossover, whatever, sample size, certain 20 features of the protocol, is appropriate for 21 adolescence and this other one is not. 22 In part, in the judgment of just acting like</p>

<p style="text-align: right;">Page 49</p> <p>1 the editor of a peer-reviewed journal, by its 2 approval and veto decisions itself, that third- 3 party governance entity, not vetoing the product, 4 but making decisions on the funding applications, 5 would be able to send signals, explicit and 6 implicit, about what sorts of study designs would 7 be better and what sorts of study designs would be 8 worse.</p> <p>9 MS. DILLEY: So just to follow up with that, 10 HEI looks at study design. It doesn't look at a 11 particular application for a particular product. 12 It's more the structure of the design.</p> <p>13 DR. CARPENTER: HEI and everything we're 14 looking at here is not something that would take 15 the place of the FDA in making decisions on this 16 product. That, I think, is quite clear. This is 17 the design and conduct of research in support of an 18 MRTTP application.</p> <p>19 MS. DILLEY: So other questions?</p> <p>20 MR. WILCOX: Thank you. Neil Wilcox, chief 21 compliance officer for the Lorillard Tobacco 22 Company. To characterize what Jim was saying in</p>	<p style="text-align: right;">Page 51</p> <p>1 My question is -- and I believe it's the 2 same thing that Jim was asking -- why can't FDA 3 hire and maintain competent individuals to know the 4 difference between well-controlled studies and to 5 make sure that the studies that are proposed by 6 industry to study and develop or generate data for 7 MRTTPs -- to make sure that the studies are well- 8 conducted?</p> <p>9 DR. CARPENTER: That's a very good question. 10 So I think I have three responses. So the FDA is 11 an old agency at some level, but this FDA is not, 12 which is to say that the Center for Tobacco 13 Products is new, and the architecture and 14 experience of reviewing applications for tobacco 15 products is also new. And the degree to which one 16 can extend FDA's past experience to this field is 17 limited in a number of respects.</p> <p>18 First of all, by the nature of tobacco 19 products themselves and the fact that they're not 20 prescribed, the FDA can't rely as heavily upon 21 prescription restrictions or labeling for 22 controlling downstream use.</p>
<p style="text-align: right;">Page 50</p> <p>1 maybe a little bit different question, the Food, 2 Drug, and Cosmetic Act requires that any studies 3 that are conducted for a product to be submitted to 4 FDA must be well-controlled.</p> <p>5 It's not new to FDA in terms of reviewing 6 proposed studies and protocols. It's what FDA 7 does, and does very well, I might add. It also is 8 not new in the arena of FDA for FDA to be 9 criticized under the notion of capture. And it's 10 not also new for the public to mistrust industry. 11 They just happen to mistrust the tobacco industry 12 even more.</p> <p>13 So with that in mind, FDA has been 14 criticized for years for capture, in other words, 15 using the studies that are generated by industry 16 to -- the data generated by studies from industry 17 to make decisions on regulating products.</p> <p>18 So FDA then must hire competent individuals 19 to make sure that when they review the protocols 20 for the intended studies, that the protocols meet 21 the requirements of the Act, and that is to be 22 well-controlled.</p>	<p style="text-align: right;">Page 52</p> <p>1 The second, of course, being that -- and I 2 think this is the key -- the public health standard 3 of the law. FDA has never been in the position, 4 before 2009, of examining studies where the 5 critical element of what is affected by the 6 treatment is not simply the individual user, but 7 also a range of other people who might be users or 8 who might quit.</p> <p>9 So that's the first thing. I agree that the 10 FDA has been at this kind of thing for a while, but 11 not in the tobacco area, and there are huge 12 differences.</p> <p>13 This is different also in another sense. 14 And I guess you're right that we had a lot of 15 discussions about this. We certainly wanted to 16 avoid turning the IOM -- we wanted this to be a 17 scientific exercise, put this way, and we wanted to 18 be consistent with the call, which is to say the 19 callout, the authorization for our activities in 20 the law.</p> <p>21 So there are two differences about this sort 22 of area of trust. Part of it is public trust in</p>

<p style="text-align: right;">Page 53</p> <p>1 the tobacco industry and scientific, and you're 2 right that there are differences. There's also a 3 difference in the way that the law has been written 4 and rewritten. And that's in Section 2, which is 5 the finding section of the Family Smoking 6 Prevention and Tobacco Control Act.</p> <p>7 There is an extensive discussion in there in 8 that, which are not findings of opinion, which are 9 not statements of judgments. Those are now, by 10 virtue of incorporation into congressionally-passed 11 and presidentially-signed statute findings at law 12 that, in fact, the tobacco industry -- and I'm 13 paraphrasing here, but read it; it's quite 14 extensive, about how this situation is different.</p> <p>15 The FDA has the expertise, but -- I choose 16 my words carefully here -- there was a pattern, as 17 I suggested here, of non-rigorous research -- not 18 saying by your company or by any other, but I'm 19 just putting it out there -- and that residue of 20 distrust that I'm talking about is in some 21 ways -- I should have mentioned it in the 22 talk -- expressed more clearly in Section 2 of the</p>	<p style="text-align: right;">Page 55</p> <p>1 be trusted. I'm just going to be frank about that. 2 I think that's where we are. Again, it's not a 3 point of blame; it's an empirical statement of the 4 status quo.</p> <p>5 MS. DILLEY: Thank you. We have time for 6 one more question.</p> <p>7 MR. DELMAN: Yes. Farrell Delman, TMA. My 8 question is somewhat similar to the last two that 9 you had in terms of the existing governance 10 structures offered by FDA, although it's slightly 11 from a different angle.</p> <p>12 As you may know, and as IOM may have 13 discussed, the FDA and NIH are offering a whole 14 series of grants to the various communities out 15 there, and the industry can participate based on 16 the webinar that has held.</p> <p>17 I guess it was August, right , Kathy?, I 18 think it was August.</p> <p>19 These are R1, R3, R21s, P50s, and so on, are 20 now being made available to address the research 21 priorities that CTP has identified, including 22 MRTPs.</p>
<p style="text-align: right;">Page 54</p> <p>1 findings than it is perhaps even in Allan 2 Brandt's -- I should apologize --but Allan Brandt's 3 book.</p> <p>4 Finally, I guess I would say that a third 5 reason that we shouldn't consider that the FDA 6 would just be in a position to weigh in on studies 7 that come from the industry is that the industry 8 itself has told us that in some very important 9 cases, adolescents and other vulnerable 10 populations, they won't conduct them. In fact, 11 that discussion that we had, and those 12 discussions -- and I'm almost certain in this 13 respect that Rutqvist was not the only one to have 14 said this at the meeting, and I've heard it 15 informally from a number of other people.</p> <p>16 When one set of companies says, "We're not 17 going to conduct these studies," it suggests, 18 number one, that you need a governance structure. 19 And it suggests, number two, that the companies 20 that do end up on their own volition and 21 organization doing studies on adolescents and other 22 vulnerable populations are probably not likely to</p>	<p style="text-align: right;">Page 56</p> <p>1 So I'm wondering what's wrong with that 2 structure. When you look at that structure that's 3 in place now, involving FDA and NIH, and a grant 4 process, and industry can contribute to it, of 5 course others would as well. And this third-party 6 NIH-FDA would be essentially identifying those 7 projects that they would wish to fund. And it runs 8 through this process that exists already.</p> <p>9 What's wrong with that process?</p> <p>10 DR. CARPENTER: Nothing is wrong with it. 11 It's just different. It's not the same thing.</p> <p>12 MR. DELMAN: No, no. But why would it not 13 be able to address the issues of governance?</p> <p>14 DR. CARPENTER: So the NIH process is not 15 for research in support of MRTP applications. It's 16 for the development of regulatory science. So it's 17 for the development of a scientific framework from 18 which a better development, evaluation, and study 19 of MRTPs generally will ensue.</p> <p>20 So let's just be very clear here. Nothing 21 in the NCI grants is funding a study that is going 22 to be used in the portfolio or dossier. I suppose</p>

<p style="text-align: right;">Page 57</p> <p>1 it's possible. That's clearly not the intent of 2 the NCI grant. They're trying to say -- by the 3 way, the FDA is doing this not just in the NCI 4 case. There's a huge development right now of 5 trying to improve regulatory science. 6 How can we develop innovation? How can we, 7 say, think about alternatives to strict randomized 8 controlled frequent trials and import Bayesian 9 criteria. How can we do a range of other things? 10 I don't think there's anything wrong with 11 the model. It doesn't solve the problem that 12 exists here, that if the companies themselves 13 conduct research, first off, most obviously, on 14 adolescents and other vulnerable populations, it 15 won't be trusted and many companies won't do it. 16 Second, that in many cases -- in part, 17 again, I want to emphasize that we think that in 18 the long run, MRTP sponsors will be better off 19 going with third-party governance than not. Their 20 research will be more credible. There is the 21 possibility -- this may seem shocking, but actually 22 Rutqvist and others point to it. There's a</p>	<p style="text-align: right;">Page 59</p> <p>1 MS. DILLEY: -- additional questions. 2 So our next presenter is David Dobbins, who 3 is the chief operating officer of the American 4 Legacy Foundation. 5 Presentation -- David Dobbins 6 MR. DOBBINS: Good morning, everybody, and 7 thanks for having us. I'm here to represent the 8 views of the American Legacy Foundation. And I 9 think we'd be remiss as a representative of the 10 public health tobacco control community not, to 11 some degree, to recognize the controversy that 12 originally erupted within that community when this 13 meeting was announced. 14 That's because, really, our substantive 15 objections to the IOM recommendation are founded in 16 the very same reasons that that reaction was so 17 poor, which is setting up a facilitated dialogue 18 between public health stakeholders and the tobacco 19 industry creates a basic false equivalency that 20 these two groups are equal partners in the public 21 health mission of the FDA Center for Tobacco 22 Products. The Tobacco Control Act makes clear the</p>
<p style="text-align: right;">Page 58</p> <p>1 possibility that through third-party governance, 2 one could get rigorous scientific collaboration 3 between academia, the tobacco companies, and their 4 scientists, and the government. 5 I don't rule that out. I'm not saying 6 that's impossible. But we're way far away from 7 that right now. And the current NCI grant system 8 is for a different purpose. 9 MS. DILLEY: So the distinction you're 10 making is the type of research that would be done 11 by a third-party governance structure to help 12 support an MRTP dossier and applications. 13 DR. CARPENTER: The research we're talking 14 about here is in support of MRTP applications. 15 What NCI is doing is, basically, how do we improve 16 the regulatory science as a whole? 17 MS. DILLEY: Great. Thank you, again. 18 DR. CARPENTER: Thanks for your questions. 19 (Applause.) 20 MS. DILLEY: Dan, you'll be here until 21 lunch, so maybe at the break, you can answer -- 22 DR. CARPENTER: Sure. Yes, yes.</p>	<p style="text-align: right;">Page 60</p> <p>1 aims of this center are to reduce the death and 2 disease related to tobacco use. 3 The letter by Dr. Ruth Malone and others 4 sets out the reason why the tobacco companies 5 cannot be considered partners or stakeholders in 6 this mission. They are adjudicated racketeers who 7 have intentionally defrauded the American public 8 for decades, which has resulted in a devastating 9 toll of preventable death and disease. The 10 credibility they have lost or the distrust towards 11 them is well-earned. 12 We share the dismay of our colleagues in 13 setting up that false equivalency, and we were 14 deeply disturbed by the initial structure of this 15 forum. It's because it plays directly into the 16 industry playbook. Trying to coop third parties to 17 get them legitimacy and to "rehabilitate their 18 image" that plays directly into their efforts to 19 whitewash their previous record, which of course 20 are based on decades and decades of evidence. 21 We note we respect the decisions of those in 22 the public health community who chose not to</p>

<p style="text-align: right;">Page 61</p> <p>1 participate in this workshop to demonstrate their 2 opposition to the FDA's approach, and we would also 3 say we don't have any substantive disagreement with 4 their concerns.</p> <p>5 The facts are clear. For many years, the 6 tobacco companies manipulated and suppressed 7 research over the course of many decades as an 8 integral part of the fraud they perpetrated on the 9 American public. But they did much of this through 10 the use of purported third-party independent 11 entities, which they actually created and 12 controlled.</p> <p>13 Based on this history, the states demanded 14 and the companies agreed, in the 1998 master 15 settlement agreement, to disband their so-called 16 third-party research arms, including the Council 17 for Tobacco Research, the Center for Indoor Air 18 Research, as well as the Tobacco Institute.</p> <p>19 If there is any doubt about the tobacco 20 industry's sordid record, it was dispelled by Judge 21 Kessler's historic and extraordinarily well- 22 documented 2006 decision, affirmed by the U.S.</p>	<p style="text-align: right;">Page 63</p> <p>1 achieving the FDA's core mission to protect the 2 public health, nor does it suggest or countenance 3 an approach by the FDA to create a false and 4 ahistorical equivalence between the industry and 5 independent science. Indeed, it is the industry's 6 record of obfuscation and fraud that drove this IOM 7 recommendation in the first place.</p> <p>8 So as you can guess, Legacy opposes that 9 part of Recommendation 10 in the IOM's report and 10 encourages the FDA to pre-approve third parties to 11 design, conduct, oversee, and/or fund the research 12 required for MRTP applications.</p> <p>13 That recommendation, while going through the 14 facts of why there is distrust towards the tobacco 15 industry, seems to ignore the implications of the 16 historic record. Thus, we believe the FDA should 17 not use its limited resources to delve into these 18 relationships, a priori approve them, and thereby 19 facilitate the tobacco company's commercial product 20 research and development activities.</p> <p>21 We believe the FDA should instead focus on 22 building its own capacity through internal and/or</p>
<p style="text-align: right;">Page 62</p> <p>1 Court of Appeals for the D.C. circuit and left 2 intact by the U.S. Supreme Court, that the major 3 U.S. tobacco companies are racketeers.</p> <p>4 With specific relevance to these questions, 5 Judge Kessler set out in great detail the company's 6 concerted strategy of the manipulation and 7 suppression of research, including the use of 8 third-party "entities" to do their bidding.</p> <p>9 We strongly recommend and concur with our 10 colleagues who have suggested that if it is not 11 already, that decision should be required readings 12 for all of the Center's staff. We should note, we 13 of course believe the tobacco companies have the 14 right to participate in the regulatory process and 15 make their views known to the FDA. I think we 16 would all agree they have aggressively done so. 17 And they have also aggressively exercised their 18 additional rights to go to court whenever the FDA 19 has acted in a way they disagree with.</p> <p>20 But let's be clear. Having a commercial 21 interest in the outcome of the FDA's decisions does 22 not make them a stakeholder or a partner in</p>	<p style="text-align: right;">Page 64</p> <p>1 external means as appropriate, to rigorously and 2 independently review MRTP-sponsored submissions, 3 seek to replicate their data as appropriate, and 4 assure that approvals are given only to 5 applications that advance the public health in 6 compliance with the statutory standards.</p> <p>7 I want to go to the IOM recommendation, and 8 it was covered pretty well with the first 9 presentation. And I want to go to why the IOM 10 recommends considering this structure. The IOM 11 grounds the recommendation in its observation that 12 the history of public distrust and the absence of 13 governance in the tobacco industry have created an 14 isolated industry that lacks not only the expertise 15 to produce the necessary range of credible and 16 reliable data, but also the trustworthiness to 17 acquire external expertise and avenues to 18 disseminate acquired data.</p> <p>19 The report explains that it raises this 20 history not out of an intent to be attributive or 21 punitive, but it's based on concern for the 22 credibility of the FDA.</p>

<p style="text-align: right;">Page 65</p> <p>1 It continues that, in so far as data 2 generated for the FDA by tobacco companies is 3 perceived to lack credibility, the FDA could find 4 its reputation, its scientific credibility, and its 5 public trust severely compromised and perhaps 6 irreversibly damaged.</p> <p>7 It recommends the solution set out in 8 Recommendation 10, which includes in part FDA 9 approval of third-party research structures, to 10 which MRTP sponsors could in effect outsource 11 product research.</p> <p>12 We should note that we take no issue with 13 the part of the recommendation, which addresses 14 MRTP sponsors' use of third parties to conduct, 15 fund, or otherwise manage their research. That, of 16 course, would be an option for them anyway, and 17 there may well be perfectly good reasons for a 18 sponsor to do that. Nor do we express an opinion 19 on the use or prior approval of third-party 20 research entities and other regulatory contexts, 21 including the development of general scientific 22 knowledge that may inform the regulatory process.</p>	<p style="text-align: right;">Page 67</p> <p>1 population as a whole, taking into account both 2 users of tobacco products and persons who do not 3 currently use tobacco products.</p> <p>4 The FDA is tasked with, and has the 5 authority, to conduct a broad and rigorous review 6 not limited to the scientific evidence submitted by 7 the applicant. The FDA will establish its 8 credibility on this issue by rigorously adhering to 9 the statutory requirements for the evaluation of 10 scientific evidence that is submitted in the 11 support of an MRTP application.</p> <p>12 Also critically important is the appearance 13 of the statutory requirement regarding the public 14 availability of applications in order to make the 15 review process as transparent as possible.</p> <p>16 On the issue of credibility, we would 17 suggest that nothing would be more potentially 18 detrimental to the FDA than allowing an entity that 19 cannot meet these fundamental statutory 20 requirements to ultimately market an MRTP to the 21 public.</p> <p>22 If the product sponsor cannot be trusted to</p>
<p style="text-align: right;">Page 66</p> <p>1 Rather, our views are confined to the IOM's 2 recommendation for FDA pre-approval of third-party 3 entities to facilitate product development 4 research. Given the unique history and challenges 5 inherent in the regulation of tobacco, we do not 6 believe that the FDA pre-approval or other sanction 7 of such third parties is an appropriate 8 use -- response to the difficulties MRTP sponsors, 9 and particularly tobacco companies, which are in 10 fact not the only possible MRTP sponsors, may 11 encounter in generating credible research.</p> <p>12 We have four reasons for opposition. First, 13 in so far that there is a problem with the 14 sponsor's submission of non-credible data, the 15 Tobacco Control Act provides an obvious and common 16 sense solution. Reject the application.</p> <p>17 Section 911(g)(1) of the Tobacco Control Act 18 squarely places the burden on the MRTP sponsor to 19 show that the product that's actually used by 20 consumers will both significantly reduce harm and 21 the risk of tobacco-related disease to individual 22 tobacco users and benefit the health of the</p>	<p style="text-align: right;">Page 68</p> <p>1 conduct reliable, replicable, and transparent 2 research, it certainly should not be entrusted to 3 sell and profit from a product that is in its 4 essence a delivery device for an addictive drug.</p> <p>5 Second, we do not believe that it is an 6 appropriate use of FDA resources, or consistent 7 with its statutory mandate, or congressional intent 8 to facilitate an MRTP sponsor's ability to make the 9 required case of approval. As mentioned earlier, 10 the findings backing up the Tobacco Control Act go 11 into this in detail. Congress understood that the 12 history of tobacco industry health claims is 13 fraught with fraud.</p> <p>14 Congress understood that light and low-tar 15 cigarettes have not only not reduced risk, but may 16 have increased tobacco use; that products that 17 purport to lower risk but do not can cause 18 substantial harm to the public health, and that 19 these risks are so high that there is a compelling 20 governmental interest in ensuring that statements 21 about modified-risk tobacco products are complete, 22 accurate, and relate to the overall disease risk of</p>

<p style="text-align: right;">Page 69</p> <p>1 the product.</p> <p>2 Thus, Congress concluded -- and I</p> <p>3 quote -- "It is essential that the FDA review</p> <p>4 products sold or distributed for use to reduce</p> <p>5 risks or exposures associated with tobacco products</p> <p>6 and that it be empowered to review any advertising</p> <p>7 in labeling for such products.</p> <p>8 "It is also essential that manufacturers,</p> <p>9 prior to marketing such products, be required to</p> <p>10 demonstrate that such products will meet a series</p> <p>11 of rigorous criteria and will benefit the</p> <p>12 population of the health as a whole, taking into</p> <p>13 account users of tobacco products and persons who</p> <p>14 do not."</p> <p>15 Third, and I'm picking up on Jed Rose a bit</p> <p>16 here, we believe the IOM report overstates the</p> <p>17 industry's isolation. It is true that a number of</p> <p>18 major research institutions do not accept tobacco</p> <p>19 industry funding, but that practice is far from</p> <p>20 uniform. Philip Morris in particular continues to</p> <p>21 be a major funder of scientific research centers.</p> <p>22 The Duke Center for Nicotine and Smoking Cessation</p>	<p style="text-align: right;">Page 71</p> <p>1 There are multiple ways that this global and</p> <p>2 wealthy industry can funnel money or other</p> <p>3 benefits, including possibilities of future work</p> <p>4 and funding, which could influence a researcher's</p> <p>5 objectivity. We are not casting aspersions on</p> <p>6 anyone to point out that trust will not be an</p> <p>7 adequate control.</p> <p>8 Finally, even assuming that one agrees,</p> <p>9 which we do not, it is the FDA's job to help</p> <p>10 provide credibility to privately-sponsored product</p> <p>11 development research. It's unclear to us how FDA</p> <p>12 pre-approval of a research structure would</p> <p>13 accomplish this. The IOM report details the</p> <p>14 scientific standards that should drive the design</p> <p>15 and conduct of studies to be included in MRTP</p> <p>16 applications.</p> <p>17 Clear guidance from the FDA to the industry</p> <p>18 on these research standards, including transparency</p> <p>19 of reporting and public availability of data, will</p> <p>20 improve the quality of studies submitted in support</p> <p>21 of an MRTP or other product-related application.</p> <p>22 FDA guidance will also provide a blueprint</p>
<p style="text-align: right;">Page 70</p> <p>1 Research is an example. Another is the University</p> <p>2 of Virginia's Tobacco Research program and, of</p> <p>3 course, we have discussed the University of</p> <p>4 California system.</p> <p>5 MRTP sponsors have vast financial resources,</p> <p>6 and we believe will have access to scientific</p> <p>7 expertise. The key is not access. It's holding</p> <p>8 those experts to time-tested standards for</p> <p>9 establishing credibility for their submissions,</p> <p>10 basing their applications on rigorous, replicable,</p> <p>11 and publicly available studies that conform to</p> <p>12 scientific standards.</p> <p>13 Fourth and lastly, the FDA must not</p> <p>14 underestimate the considerable difficulties it</p> <p>15 would encounter in assuring that a researcher or a</p> <p>16 research entity is truly independent of the tobacco</p> <p>17 companies whose product development research it</p> <p>18 would be conducting. After all, this is an</p> <p>19 industry that with tragic results has decades of</p> <p>20 experience in establishing and then expertly</p> <p>21 obfuscating its relationships with the front</p> <p>22 organizations that have done its work.</p>	<p style="text-align: right;">Page 72</p> <p>1 for review of MRTP applications, either internally</p> <p>2 or via FDA contractors, to ensure that the data and</p> <p>3 results provided by MRTP sponsors meet standards</p> <p>4 for scientific rigor. An FDA's certificate of</p> <p>5 approval of a particular entity, review board, or</p> <p>6 scientist, before any research is even designed,</p> <p>7 conducted, or conceived, would seem to be, at best,</p> <p>8 irrelevant to review processes in the particular,</p> <p>9 and, at worst, indicative of a bias towards</p> <p>10 approving whatever is submitted.</p> <p>11 Thank you so much for your consideration of</p> <p>12 our views.</p> <p>13 (Applause.)</p> <p>14 MS. DILLEY: Thanks. What we want to do is,</p> <p>15 as I said before, for the panel, we'll take one or</p> <p>16 two questions for clarification. And then, at Q&A,</p> <p>17 we'll have all panel members from this panel.</p> <p>18 (Inaudible -- off mic.). So are there any</p> <p>19 questions?</p> <p>20 (No response.)</p> <p>21 MR. DOBBINS: Thank you.</p> <p>22 MS. DILLEY: So next, we have Joanna Cohen,</p>

<p style="text-align: right;">Page 73</p> <p>1 who is the Bloomberg professor of disease 2 prevention and the director of the Institute for 3 Global Tobacco Control at Johns Hopkins Bloomberg 4 School of Public Health. 5 I also want to remind people, on saying 6 titles and affiliations, that their bios are 7 out -- when you came in -- if you want that 8 information, it's available out at the front desk 9 for your interest, if you'd like to review that. 10 So with that, I'll turn it over to 11 Dr. Cohen. 12 Presentation -- Joanna Cohen 13 DR. COHEN: Great. Thank you. 14 Thank you for the opportunity to speak. Let 15 me cut to the chase and tell you my position, and 16 then I'll go through some of the slides that I've 17 prepared. So, basically, I feel that there needs 18 to be a governance structure for MRTP and other 19 research that is going to be considered by the FDA 20 for the regulation of tobacco products, but I don't 21 agree with the Recommendation 10 as put out 22 directly in the IOM report.</p>	<p style="text-align: right;">Page 75</p> <p>1 schematic from that article that shows a diagram of 2 how tobacco companies can have links with academia. 3 So one is through research grants directly to 4 researchers. There's, of course, donations that go 5 to academic institutions, and as well ties on 6 boards of governors with appointments of tobacco 7 company officials on academic boards. 8 So a couple years later, I wrote an 9 editorial in the British Medical Journal, 10 Universities and Tobacco Money, indicating clearly 11 that universities are accomplices in the tobacco 12 epidemic. 13 So there's been a broader recognition -- or 14 with a broader recognition that the tobacco 15 companies have been vectors of the tobacco 16 epidemic, there were several efforts to convene 17 researchers, and policy experts, and civil society 18 to debate the issues regarding tobacco industry 19 involvement and research. 20 Mitch Sellers referred to a couple of them. 21 Associated with the 2003 SRNT meeting in New 22 Orleans, there was a post-conference symposium that</p>
<p style="text-align: right;">Page 74</p> <p>1 I am in my 20th year now of doing tobacco 2 control research. I have many interests. And one 3 of them is the links between tobacco companies and 4 academia. 5 I'll tell you why I got interested in this, 6 and this was back in the 1990s, when I was working 7 in Canada. And at that time, there was a move to 8 ban tobacco company sponsorship of sporting and 9 cultural events. And we would point to those 10 sports groups and point to the cultural groups that 11 took tobacco company donations and said how awful 12 that was. And I thought, well, before we point 13 fingers at others, we need to look at the dirt in 14 our own home. 15 That's why I got interested in how 16 universities were basically accomplices in the 17 tobacco epidemic. And one of the commentaries that 18 I wrote, published in 1999, was Institutional 19 Addiction to Tobacco. 20 I think these aren't my updated slides. Is 21 there another -- let me just see. 22 I have a schematic that shows -- so I have a</p>	<p style="text-align: right;">Page 76</p> <p>1 discussed this. And I actually -- and I guess the 2 slide isn't -- oh, okay. Here it is. 3 This is the schematic that shows the links 4 between the tobacco industry with researchers, 5 industries, and boards of governors. I've 6 addressed those, and they're in the paper. 7 I wrote one of the background documents for 8 that meeting in New Orleans, and it was published 9 in the TRDRP newsletter in 2003 that outlined some 10 of the issues regarding tobacco industry 11 sponsorship of research. 12 There was also a session held at the 2005 13 meeting, SRNT meeting, in Prague -- and I'll just 14 say SRNT is the Society for Research on Nicotine 15 and Tobacco -- and a session associated with the 16 2005 National Conference on Tobacco, Our Health, 17 held in Chicago. 18 But I think a number of us got a little 19 frustrated because we felt we were preaching to the 20 choir, and there's lots of talk and not enough 21 action on this front. So in 2007, my colleagues, 22 including one who's in the room today and others,</p>

<p style="text-align: right;">Page 77</p> <p>1 convened an invitation-only workshop at the 2007 2 SRNT meeting in Austin, where we wanted to discuss 3 various funding models of tobacco-sponsored 4 research and criteria to involve, amend. So the 5 start of that meeting was, is there a funding model 6 where tobacco company money would be used for 7 research that would be acceptable to the tobacco 8 control community? 9 We didn't come with a pre-supposed answer. 10 We did not invite tobacco company employees to that 11 meeting, but we did make sure to have a range of 12 views represented at that meeting, including people 13 who accepted tobacco company money for research, as 14 well as people who were strongly opposed to that. 15 So this is the paper that was published 16 based on that meeting, where, based on the 17 discussions and the feedback, we proposed some 18 criteria for evaluating tobacco control research 19 Funding programs with financial support from the 20 tobacco industry. 21 Of course, all this work and a publication 22 of the paper occurred before the Center for Tobacco</p>	<p style="text-align: right;">Page 79</p> <p>1 there is an acknowledgement that a funder can 2 influence an agenda even when there are no strings 3 attached. So there is a sense of obligation and 4 awareness of priorities and possibly expectation of 5 future funding. And, of course, this particular 6 criteria is going to be a little more challenging 7 with Section 911 because the agenda is sort of set. 8 But this is one of the general criterias that we 9 outlined. 10 We talked about governance sort of broadly, 11 proposed a transparent and effective governance 12 structure to oversee the funding that took place. 13 We also thought that there needed to be adequate 14 protections in place to guard against potential 15 conflicts of interest. There would be a written 16 conflict of interest policy, mechanisms for 17 enforcing that. And not only would there be 18 disclosure of potential conflicts of interest, but 19 also some relationships might have to be 20 prohibited. 21 So there's a huge challenge with tobacco 22 industry funding, that this research -- and my</p>
<p style="text-align: right;">Page 78</p> <p>1 Products was even a -- well, it was probably a 2 twinkle in the eye by then, but certainly not set 3 up in before the passage of the Family Smoking 4 Prevention and Tobacco Control Act. 5 So let me just go through the eight criteria 6 that we laid out. And I want to acknowledge that 7 there is overlap between the criteria as well as 8 they are pretty generic and can be applied to a 9 broad range of research. 10 So transparency and independence. So the 11 funding mechanism needed to be transparent and 12 independent with an application process that was 13 explicit and clear with scoring criteria, of course 14 with peer review, and reviewers would not be 15 tobacco company employees or contractors. The 16 funding process had to be competitive, again, with 17 using peer reviewers with relevant experience. So 18 this is not sole-source funding. 19 Clearly, there would have to be provisions 20 for ownership of data and freedom to publish 21 results. The research agenda would have to be set 22 independently of the tobacco companies because</p>	<p style="text-align: right;">Page 80</p> <p>1 colleagues have addressed it -- has been used for 2 public relations gains that counteract public 3 health. So companies have gained respectability 4 and credibility by association in funding this 5 funding research. So the funding model would have 6 to ensure that there is minimization of the PR 7 gains that counteract public health. 8 Then our last criterion at the time, because 9 this was thinking within a vacuum at the time, was 10 that the model had to -- one of the criteria was 11 that it had to be feasible that it could actually 12 happen. 13 So we applied these criteria to four 14 different models -- it's in the paper, so I won't 15 go through it -- and then we held another meeting 16 at the 2010 SRNT meeting to discuss the criterion 17 and see what the next steps were. And at that 18 point, we knew about the new tobacco act, and we 19 put things on hold for a bit. 20 But let me just go through the criteria in 21 the IOM report that are laid out for the design and 22 structure features of a TRGE, which is one of those</p>

<p style="text-align: right;">Page 81</p> <p>1 new acronyms that is a mouthful. So that was a 2 tobacco research governance entity. I think that's 3 the terminology used in that report. So the 4 criteria that the IOM report lays out is that the 5 funding could be public and private funding. There 6 would be an oversight board that would be 7 independent of the FDA and tobacco or MRTTP 8 companies, and there would be conflict of interest 9 policies.</p> <p>10 The research design would be independent of 11 the sponsor. There would be organization, 12 oversight, and training, so the research 13 performance would be monitored. There would be IRB 14 training and data monitoring committees. And there 15 would have to be some sort of contract mechanism, 16 either a request for applications or a contract. 17 And there would be quality control, including 18 audits.</p> <p>19 So I just put together a paper or a table to 20 try to compare the IOM features of a governance 21 structure and the ones that we had thought about. 22 So the funding, we dealt with separately. The</p>	<p style="text-align: right;">Page 83</p> <p>1 still, even with this, need to be critically 2 evaluated by the FDA and CTP. So just because we 3 have this structure in place, it doesn't mean that 4 this is gold standard science. It still needs to 5 be critically evaluated.</p> <p>6 If, for once, a third party structure is set 7 up, its structure and processes need to be reviewed 8 regularly. There needs to be periodic external 9 oversight and review by a prestigious external 10 group, would also be important.</p> <p>11 A couple of additional issues to consider. 12 We do not want to be in a situation where the 13 American taxpayer subsidizes research and 14 development work for tobacco products. So whereas 15 the IOM talks about public and private funding, I 16 don't see public funding going into this type of 17 funding model.</p> <p>18 I think a proportion of the research funding 19 budget of a funding model of this kind should be 20 spent on broader tobacco control research beyond 21 MRTTPs and perhaps even on important topics that are 22 outside the direct mandate of FDA. And there are a</p>
<p style="text-align: right;">Page 82</p> <p>1 oversight board corresponds to the general 2 governance that we talked about in protection 3 against conflicts of interest.</p> <p>4 The research protocol advice that the IOM 5 suggested, we wrote up as transparency and 6 independence, including an independent research 7 agenda. We didn't discuss explicitly organization, 8 oversight, and training, whereas the IOM talked 9 about contract mechanisms. We were very clear 10 about a competitive funding process.</p> <p>11 We didn't address quality control per se, 12 and then we talked about things like ownership of 13 data, freedom to publish, and addressing and 14 minimizing industry PR gains that counteract public 15 health that were not explicitly addressed in the 16 IOM report.</p> <p>17 So a couple of concluding remarks. From 18 what I can tell in the IOM report, it talked about 19 independent third parties, plural, so my proposal 20 is for one governance body to oversee all 21 CTP-related product research. I'm not sure what 22 exactly pre-approval means, but all research will</p>	<p style="text-align: right;">Page 84</p> <p>1 number. And then the funding mechanisms and 2 governance structures need to be acceptable to the 3 tobacco control community, so these discussions 4 really need to continue, and a lot of thinking is 5 still needed to work through these issues.</p> <p>6 So I think that's it for me.</p> <p>7 MS. DILLEY: Thank you. Thanks very much.</p> <p>8 DR. COHEN: Sorry. There were a couple of 9 others. I think Daniel had this as well. It's 10 been a while since I've seen the slides.</p> <p>11 So I'll just say -- I mean, all this is 12 really important because -- credibility of the 13 research was mentioned before. The researcher 14 needs to be credible, and I think my colleagues 15 will address this further, but there are certainly 16 challenges of taking tobacco company money for 17 research. And we don't want the same people doing 18 the -- the same old folks doing this type of work. 19 And we want our colleagues to be credible members 20 of the tobacco control research community, even if 21 they're doing some important work in this area.</p> <p>22 More and more journals are not accepting</p>

<p style="text-align: right;">Page 85</p> <p>1 articles that are sponsored with tobacco company 2 money. We've talked about institutions that don't 3 take tobacco money. So we want to make sure that 4 the researchers remain credible and not ostracized 5 from the community. The research itself has to be 6 credible because, if it isn't, the credibility of 7 the Center for Tobacco Products and, more broadly, 8 the FDA is at stake.</p> <p>9 So, again, the funding model and governance 10 structure needs to be thought out very clearly, a 11 lot more discussion, and I think imperative that we 12 figure out a model that is acceptable to the 13 tobacco control community so that we can move 14 forward together.</p> <p>15 (Applause.)</p> <p>16 MS. DILLEY: A couple of questions for 17 Joanna before we go to break?</p> <p>18 DR. CARPENTER: I'm generally loud enough 19 that I don't need one of these. The slide where 20 you say what the entity will do, are you 21 contemplating an entity that sets up rules for the 22 conduct of research or a third-party entity that</p>	<p style="text-align: right;">Page 87</p> <p>1 question, and I think I have to think through that 2 carefully. As I sort of hinted, I would like to 3 see this as broader, and not just -- potentially 4 could see a funding model that actually funds other 5 very important public health research and provides 6 a mechanism for that.</p> <p>7 So while contributions go towards looking at 8 the minutia of product changes, we can also do some 9 of the population health work that needs to be 10 done.</p> <p>11 MS. DILLEY: That's the public health 12 research, but that scope is broader than the MRTP 13 research we're talking about.</p> <p>14 Anybody else have a question for Joanna? 15 (No response.)</p> <p>16 MR. DILLARD: Jim Dillard, Altria Client 17 Services. Dr. Cohen, thank you. I had a question, 18 actually, for FDA and then perhaps a question for 19 you, which is, it appears from an industry 20 perspective, as I'm thinking about -- sort of 21 applications, as an example, you would think about 22 perhaps having to do some sort of clinical</p>
<p style="text-align: right;">Page 86</p> <p>1 conducts that research itself through employees, 2 grantees, et cetera?</p> <p>3 DR. COHEN: No. I see the FDA is setting up 4 the rules for the research. And this third party, 5 as I see it -- and this just starting points, so 6 this needs a lot more discussion. But as I would 7 see it, they would not conduct the research. It's 8 just a flow-through for a competitive funding 9 process.</p> <p>10 So money would be put into this funding 11 model with the governance structure. When there's 12 research to be done, people can apply, and then 13 it's a structure to review who can do the research 14 and what the strongest proposals are.</p> <p>15 DR. CARPENTER: That's what I thought. And 16 just one brief follow-up -- and I won't go into 17 part B -- what advantages would that third-party 18 entity provide, over the FDA issuing contracts for 19 research, that it wanted to follow up through 20 approved government funding mechanisms such as 21 grants or contracts?</p> <p>22 DR. COHEN: Yes. That's a really good</p>	<p style="text-align: right;">Page 88</p> <p>1 research, perhaps in a substantial equivalence type 2 of application, definitely in a 910 new product 3 application or a 911 MRTP application, where 4 industry would be thinking about research to 5 support an application for a product where it will 6 meet the statutory criteria, but also perhaps be of 7 some benefit both to public health as well as 8 industry interests as well.</p> <p>9 So the question I'm having going through my 10 head is, are we talking about here a broader topic 11 of third-party governance or governance just for 12 the purpose of an MRTP application? Because what I 13 could envision potentially -- and maybe this is 14 what you were getting at a bit, Dr. Cohen -- is 15 that there could be different models for different 16 application purposes, the model that you put 17 forward, the model that the IOM put forward.</p> <p>18 So one of the questions I've got for the 19 agency is, are we talking broadly about third-party 20 governance or are we talking about it more 21 specifically for an application type of purpose? 22 Which is where my head was when I came in here.</p>

<p style="text-align: right;">Page 89</p> <p>1 MS. DILLEY: You mean as specific, this 2 workshop? 3 MR. DILLARD: Yes. 4 MS. DILLEY: So the frame is around the MRTP 5 report, but I think -- and we've already gone there 6 to think more broadly. 7 So the starting point is the MRTP report and 8 the IOM's report on the third-party governance, 9 but, clearly, it's not a big leap to go more 10 broadly, if you want to address that. 11 So one more -- we'll take a break a little 12 bit early, and that actually would be helpful, 13 because we have a panel of three speakers as 14 opposed to two for this section. So we're happy to 15 take a break early. But one more question, and 16 then we'll take a break. 17 MR. ROSE: Jed Rose again. 18 MS. DILLEY: Could you use the mic? People 19 are watching on line. And also, a warning for 20 those of you who ask questions and speakers, 21 they're asking for interpretation -- which you 22 already did, Joanna, so thank you -- of acronyms.</p>	<p style="text-align: right;">Page 91</p> <p>1 answer I can give you at this point. 2 MS. DILLEY: I assume that's where the 3 criteria came from in terms of just what it might 4 look like to at least start that conversation. 5 Why don't we take a break? It's 20 after. 6 I want to thank Joanna again, David, and Daniel 7 Carpenter. And we will resume at 25 of. 8 (Whereupon, a recess was taken.) 9 MS. DILLEY: If everyone could take their 10 seats, we'll get started. Just two quick comments. 11 One is I neglected to mention in the overview of 12 the agenda earlier, that there's one error on that. 13 Tomorrow, for the time, you'll see at the break, 14 you thought you were getting a really long break, 15 10:00 to 10:45, but in fact, that's only 15 16 minutes. 17 So that should be 10:15. I mean, that's 18 important because, obviously, to try and put five 19 speakers in an hour was going to be challenging. 20 So we just added a half an hour to that. 21 So just so you know, in case you had 22 elaborate plans for that break, you have to change</p>
<p style="text-align: right;">Page 90</p> <p>1 So any acronyms, please say what it is first, and 2 then you can use it. 3 MR. ROSE: Jed Rose. Could you just 4 elaborate a little bit more on what you might mean 5 by the various standards being acceptable to the 6 tobacco control community? Because there's quite a 7 diversity of opinions within the "tobacco control 8 community." 9 Are you thinking of a majority vote, or what 10 does it mean to be acceptable to -- we obviously 11 want to avoid any kind of groupthink mentality. So 12 what would that mean? 13 DR. COHEN: Thank you, Jed. And I want to 14 thank you for being part of this meeting and an 15 active participant in the meeting that led to the 16 paper on the criteria, so thank you for being 17 there. I mean, that's a rhetorical question. It's 18 good to have diversity of views. I'm glad that the 19 FDA is starting to discuss this and has initiated 20 this discussion. And I think it's going to take 21 more discussion to figure out -- to debate and to 22 think about how to move forward, so that's the best</p>	<p style="text-align: right;">Page 92</p> <p>1 them. So 10:00 to 10:15. 2 I just wanted to mention that, and also just 3 remind people, please, there are about, I think 4 somebody said, about 95 people listening by 5 webcast, and they really are asking for 6 clarification on any acronyms used, which any area 7 is riddled with that. But if people could give the 8 full name, and then, if you want, for the rest of 9 your comments to use acronym, that's fine. 10 So next up, we have Matt Myers, who is the 11 president for the Campaign for Tobacco-Free Kids. 12 And, again, then we'll go on to Mark Parascandola 13 and Eric Donny before we take a break for lunch. 14 So, Matt, with that, we'll turn it over to 15 you. 16 Presentation -- Matthew Myers 17 MR. MYERS: Thank you, Abby, and thanks to 18 all of you at FDA for holding this session. The 19 advantage and disadvantage of not being the first 20 speaker is, I'm going to try to adjust a little bit 21 what I say so that I just don't repeat what 22 everybody else has said in that respect. So I</p>

<p style="text-align: right;">Page 93</p> <p>1 apologize if there's one or two things that appear 2 less smooth as a result of it in that respect. 3 But let me summarize our conclusions at the 4 Campaign for Tobacco-Free Kids. First, Section 911 5 of the Family Smoking Prevention and Tobacco 6 Control Act does address a very critical issue. 7 And that is that for more than 50 years, the 8 tobacco industry has used the promise of 9 potentially less hazardous products, not to 10 actually reduce risk or reduce the number of people 11 who die from tobacco use, but to keep their market 12 share and to keep people smoking with what we now 13 know are truly tragic results. And that is more 14 people smoking, fewer people quitting, and 15 literally millions more people dying as a result of 16 the conscious direct decisions of the tobacco 17 industry about how it is used, the whole potential 18 of the Holy Grail of a less hazardous tobacco 19 product. 20 Section 911 doesn't prejudge whether there 21 is actually a role for modified-risk tobacco 22 products. What it does is seek to impose for the</p>	<p style="text-align: right;">Page 95</p> <p>1 applications. We think that there is an inherent 2 conflict with regard to that. 3 The tobacco industry's abuse of science, the 4 scientific process, third-party institutions, and 5 some of our nation's most credible scientists at 6 this point, is beyond debate, and it is part of the 7 elephant in the room any way you cut it. 8 For 50 years, the tobacco industry has 9 claimed to be interested in rigorous science. It 10 has claimed to be interested in reducing the number 11 of people who die from using its product. It has 12 claimed to be interested in supporting independent 13 third-party research as we go on. 14 Time after time, however, the evidence now 15 demonstrates that they've corrupted science, 16 they've produced products that people have believed 17 are less hazardous, but have done nothing more than 18 keep people smoking. And to a degree that many of 19 us would like to think is impossible, they have 20 corrupted some of our most credible institutions, 21 not because those institutions are bad but because 22 those institutions didn't recognize the extent to</p>
<p style="text-align: right;">Page 94</p> <p>1 very first time in our history a rigorous 2 scientific standard and set of criteria to address 3 that issue, so that we're no longer at the whim of 4 an industry that has been willing to say and do 5 anything to keep people smoking without regard to 6 the health consequences of that. That's the 7 history. That's what brings us to this point in 8 our time. We lose sight of that history at our 9 peril. 10 Second, we at the campaign strongly endorse 11 11 of the 12 proposals by the Institute of 12 Medicine, those proposals that focus on the 13 scientific criteria, proposals 1 through 9, about 14 how studies should be conducted, the type of 15 studies that should be conducted, the type of rigor 16 that ought to be applied to studies that should be 17 conducted. 18 Having said that, we do not support IOM 19 recommendation, at least the component of it that 20 focuses on pre-approving independent third parties 21 to the extent that it relates to research tied to 22 specific MRTP, modified-risk tobacco product,</p>	<p style="text-align: right;">Page 96</p> <p>1 which an industry was willing to go to promote its 2 product without regard to the consequences. 3 Therefore, it is our view that, if IOM 4 Recommendation 10 is intended to provide 5 pre-approval to an independent entity linked to a 6 specific NRT application, then we think it is a 7 fundamental idea and, in the long run, will end up 8 undermining FDA's authority, as David Dobbins had 9 said. 10 I don't want to spend a lot of time quoting 11 all the things. I have submitted to the FDA a much 12 longer document that tries to lay out the things. 13 But the things I'm saying are not in dispute, as 14 Judge Kessler found. Over the course of 50 years, 15 defendants -- and by that we mean many of the same 16 companies who are in the room today -- lied, 17 misrepresented, and deceived the American public, 18 including smokers and the young people they avidly 19 sought as replacement smokers, about the 20 devastating health effects of smoking and 21 environmental tobacco smoke. 22 How do they do it? Judge Kessler found that</p>

<p style="text-align: right;">Page 97</p> <p>1 they suppressed research. They destroy documents. 2 They manipulated the use of nicotine so as to 3 increase and perpetuate addiction. And they abused 4 the legal system in order to achieve their goal, to 5 make money with little, if any, regard for 6 individual illness or suffering, soaring healthcare 7 costs, or the integrity of the legal system. 8 That's the context in which these decisions 9 get made. We would all like to believe that we 10 live in a utopia, but that's not the situation. 11 We'd all like to believe that there is an industry 12 out there who really shares, at least at some 13 level, a concern about the public health. But you 14 can go back as far as the original, the original 15 frank statement made by the tobacco industry 50 16 years ago, over 50 years ago, in which they said, 17 "We are committed to sound science. We will 18 promise you an open and transparent process. We 19 will promise you that we will act on that science." 20 We can show you quote after quote from 21 tobacco industry executives that, "If it can be 22 proven that our products cause lung cancer, of</p>	<p style="text-align: right;">Page 99</p> <p>1 concerning the scientific process, that guarantees 2 openness, that guarantees transparency, that 3 provides the best possible protection to the FDA, 4 that the tobacco industry once again hasn't 5 manipulated the scientific process, the scientific 6 methods, or carefully, as they have so often in the 7 past, designed experiments that they already knew 8 the answers, and therefore were simply producing 9 data to continue to distort the true scientific 10 truth as we move forward. 11 I don't see and we don't see a reason for 12 FDA to set up a special set of rules for the 13 tobacco industry. The reality is that when anybody 14 has tried to do that, it has become the tobacco 15 industry's roadmap to continue its deception. 16 That's not the job of the FDA. 17 Professor Carpenter talked about how other 18 industries have adjusted in the past when new rules 19 concerning pre-approval came in to place. This 20 isn't a new concept, although it's new to the 21 tobacco industry. 22 Yes. In the pharmaceutical industry, some</p>
<p style="text-align: right;">Page 98</p> <p>1 course we wouldn't sell them." 2 What does that demonstrate for the process 3 we've got here? It demonstrates that, in fact, 4 while Professor Carpenter can say carefully, "We're 5 not assigning blame for the lack of trust," indeed, 6 if we fail to recognize the source of the lack of 7 trust, then we are really truly fools after a fool 8 errand, not willing to learn from history. 9 You're going to hear tomorrow, as we've 10 heard for a year now, that the tobacco industry is 11 once again truly concerned about independence. No 12 one should be fooled. No one should believe it. 13 It is actions that need to count in this case. 14 They have mastered the words. They have 15 said them time and time again. And nonetheless, 16 time and time again, what we have seen is that they 17 have been willing to corrupt science, scientists, 18 and scientific institutions. 19 Therefore, what is our recommendation? 20 FDA's top priority should be to establish rigorous 21 scientific standards that all applications under 22 Section 911 should meet, including governance</p>	<p style="text-align: right;">Page 100</p> <p>1 companies develop truly credible institutions for 2 pre-approval and others did not. And the ones that 3 did not, did not survive, but that is the way the 4 marketplace is designed to work when we put a 5 priority on saving lives and health. It should be 6 the same case here. 7 There are, however, even when you do that 8 comparison, some important distinctions between how 9 the pharmaceutical industry responded to pre-market 10 approval and the tobacco industry, that are 11 relevant to this consideration. I think that's 12 important. 13 As Professor Carpenter in his book said, 14 whatever the tension is between the FDA and the 15 pharmaceutical industry -- and this isn't a direct 16 quote, so, Dan, I apologize if I get the thrust 17 wrong, but I don't think so. What he said was that 18 the pharmaceutical industry knows that it cannot 19 survive if it loses credibility with the American 20 public or with the regulating agency. Thus, it has 21 a great deal at stake in maintaining that 22 credibility.</p>

<p style="text-align: right;">Page 101</p> <p>1 The tobacco industry, on the other hand, has 2 been able to sell its product to the public even 3 though there is no industry held in lower esteem. 4 Why? Because its primary market is kids, its 5 product is addictive, and it has been able to work 6 behind closed doors to ensure that that addiction 7 is all powerful, moving forward. 8 Second, the tobacco industry has already set 9 a very different tone with the FDA, not the one 10 you're going to hear tomorrow. But the truth is, 11 the facts already show that tone. They will not 12 depend on credibility with the institution. 13 They'll depend on fear. They will sue the 14 FDA -- and they have demonstrated it already -- the 15 second the FDA does something not wrong, but that 16 threatens their marketplace. So the facts don't 17 show a changed industry. 18 The facts don't show a changed industry. 19 The facts show an industry working off of the same 20 game plan that we have seen for decades, and 21 decades, and decades. 22 There are real values to an independent</p>	<p style="text-align: right;">Page 103</p> <p>1 marketing is designed to make tobacco products and 2 different tobacco products highly appealing to 3 young people, attractive to young people because 4 they know what we know. And that is, if they don't 5 catch them young, they're probably never going to 6 catch them. 7 That leads us to the last conclusion, and I 8 think this is a very important distinction between 9 the tobacco industry and the other industries 10 regulated by FDA. And that is, FDA was created and 11 looks at pharmaceuticals to solve problems that 12 aren't caused by the pharmaceutical industry. 13 Therefore, the path of producing drugs is critical 14 to solving a problem that would otherwise exist. 15 The Center for Tobacco Products is dealing 16 with an industry that is the cause of the death and 17 disease and whose financial interests, to this 18 point in time, they have always perceived to be, 19 "How many products can we sell," not, "How safe are 20 those products?" So it is a very different kind of 21 interaction. The pharmaceutical industry will 22 thrive on solving a problem. To date, the tobacco</p>
<p style="text-align: right;">Page 102</p> <p>1 third-party advisory body on research to look at 2 broad questions, to look at the industry tactics 3 that have made their products so appealing to 4 adolescents, and to look at the kind of marketing 5 that they continue to do that makes their products 6 appealing to adolescents. But not to provide a 7 roadmap that says, "This product is okay and is not 8 going to be used by an adolescent." 9 There's another critical fact that goes to 10 that, and that is -- Professor Carpenter talked to 11 us, that there is a unique component to this 12 legislation that requires you to look at not just 13 the toxicity of the product, but whether that 14 product is going to appeal to a broader range of 15 the population. And the research under Section 911 16 can't just focus on the product narrowly. It also 17 has to focus on how it's going to be marketed, 18 which is truly a different thing, as you look about 19 this. 20 One product could be marketed truly to 21 adults, but the reality itself up to this point in 22 time is virtually all of the tobacco industry</p>	<p style="text-align: right;">Page 104</p> <p>1 industry has thrived by causing the problem. 2 So the notion that we can expect the tobacco 3 industry suddenly to turn around, and change its 4 stripes, and become part of the solution is 5 something we should look at with a great deal of 6 hesitancy. There is nothing we have seen in the 7 tobacco industry's response to this act, to their 8 rhetoric, or to their behavior, that says it's time 9 for us to trust them. It is time for us to ensure 10 that we have a regulatory agency that operates 11 independently but fairly, rigorously, with one goal 12 in mind, and that is, "What actions will save the 13 most lives, not promote the most products?" 14 If the tobacco industry can meet those 15 standards, then fine. If it can't meet those 16 standards, then Section 911's main contribution may 17 well be simply to prevent them from continuing to 18 do what they have done for 50 years, which is use 19 the hope of a potentially less hazardous product to 20 keep people smoking. Thank you. 21 (Applause.) 22 MS. DILLEY: So we just have time for one or</p>

<p style="text-align: right;">Page 105</p> <p>1 two questions.</p> <p>2 Can I ask you a question?</p> <p>3 MR. MYERS: Sure.</p> <p>4 MS. DILLEY: It seemed like the combination</p> <p>5 of third-party governance that you mentioned has a</p> <p>6 role in some things, but the combination of</p> <p>7 pre-approval by FDA and the fact that it supports</p> <p>8 an application is where there is a particular</p> <p>9 problem.</p> <p>10 MR. MYERS: Exactly. I think, if you do it,</p> <p>11 is linked to a specific application. What we've</p> <p>12 already seen is that those of us who have been</p> <p>13 concerned about what application has been filed,</p> <p>14 that process isn't transparent until too late in</p> <p>15 the process. If it was going to be an open and</p> <p>16 transparent process, maybe there would be something</p> <p>17 that one could talk about. But right now, it</p> <p>18 operates behind closed doors until very late in the</p> <p>19 process.</p> <p>20 Second, I think that there is an inherent</p> <p>21 conflict. And what we have seen is, in this case,</p> <p>22 when somebody identifies an institution -- Harvard</p>	<p style="text-align: right;">Page 107</p> <p>1 Dobbins's -- thanks -- primary concern is about the</p> <p>2 idea, basically, the FDA approving these third-</p> <p>3 party governance organizations or institutions, and</p> <p>4 that the concern is a little bit less with the idea</p> <p>5 that there should be some separation of tobacco</p> <p>6 funding and the actual research or the research</p> <p>7 institution that's conducting it.</p> <p>8 Is that an understanding of where your</p> <p>9 primary objection -- I'm not speaking for him, but</p> <p>10 the primary objection to Recommendation 10.</p> <p>11 MR. MYERS: Yes. I can't speak for David.</p> <p>12 Pre-approval is our highest priority in terms of</p> <p>13 the concerns with regard to that. I would think</p> <p>14 that there would be issues that relate to "a</p> <p>15 specific narrow product" as opposed to some broader</p> <p>16 use of the third-party funding for a broader set of</p> <p>17 questions that will relate to the issue of</p> <p>18 Section 911, so that you can address them broadly.</p> <p>19 In the examples you talked about where the</p> <p>20 industry said -- and I can't speak to Swedish</p> <p>21 Match, but I've heard industries say before, "Gee,</p> <p>22 we don't do research on young people because that</p>
<p style="text-align: right;">Page 106</p> <p>1 is a fabulous example for Dan, incredible</p> <p>2 institutions. I mean, NCI after the first Surgeon</p> <p>3 General's report came out, we had the Tobacco</p> <p>4 Working Group, a process that got incredibly</p> <p>5 corrupted, focused on less hazardous cigarettes</p> <p>6 rather than focusing on what are the harms caused</p> <p>7 and how do we stop them.</p> <p>8 So we all like to think that we can build</p> <p>9 institutions that are impenetrable to corruption,</p> <p>10 but you can't do it when you have an industry with</p> <p>11 a mindset, that our sole goal is how do we maximize</p> <p>12 our profit, no matter how many people we kill? And</p> <p>13 to this date, that's what the tobacco industry's</p> <p>14 mindset has been.</p> <p>15 MS. DILLEY: One other question, Dan, and</p> <p>16 then we'll go on to the next.</p> <p>17 DR. CARPENTER: Thanks for the excellent</p> <p>18 talk. I just want to clarify, because I think what</p> <p>19 I'm understanding is your -- and I'm forgetting the</p> <p>20 gentleman who spoke earlier before --</p> <p>21 MR. MYERS: David Dobbins</p> <p>22 DR. CARPENTER: -- David</p>	<p style="text-align: right;">Page 108</p> <p>1 would be unethical," only for us to discover in</p> <p>2 their own internal documents just the opposite.</p> <p>3 But I do think that there is a role to play for</p> <p>4 maybe a third party to look at. What parameters</p> <p>5 would we have to put on it to make sure that it</p> <p>6 didn't impact young people in that respect and come</p> <p>7 up with a set of guides. My suspicion is, if the</p> <p>8 tobacco industry didn't like the results, they</p> <p>9 would attack them, too.</p> <p>10 DR. CARPENTER: Yes. So I want to just</p> <p>11 follow up just to clarify a little bit of what my</p> <p>12 own thinking is on this. First off, I think it's</p> <p>13 quite possible you'll still disagree with what I</p> <p>14 have to say and that Mr. Dobbins will as well.</p> <p>15 But I think just one quick thing is, number</p> <p>16 one, I think the recommendation is sufficiently</p> <p>17 general as to include, as possibilities, for</p> <p>18 instance, what Dr. Cohen presented earlier, the</p> <p>19 idea that what really is being approved here is at</p> <p>20 some level a larger entity, to which could become</p> <p>21 kind of the go-to model for individual product</p> <p>22 funding decisions and things like that. I'm not</p>

<p style="text-align: right;">Page 109</p> <p>1 recommending that as the only thing, but the IOM's 2 practice in many cases such as these is not to 3 pinpoint a very, very particular kind of model to 4 be used. 5 So I think what may be kind of inducing some 6 disagreement is the plural here, the idea that the 7 third-party institutions or the third-party 8 organizations, as opposed to a general HEI-like 9 organization, should be in operation. 10 So I want to emphasize that it's not 11 necessarily the case that the recommendation would 12 set up 200 different third-party institutions. It 13 is quite possible that it's consistent with just 14 one. 15 But I want to emphasize one other thing 16 about -- and this is just an argument against or at 17 least to sort of temper a little bit of the doubt 18 about pre-approval. 19 We thought about this. At some level, this 20 entire regulatory structure, not just Section 911, 21 places the FDA in a situation where the credibility 22 of an institution that, relative to a wide variety</p>	<p style="text-align: right;">Page 111</p> <p>1 revelatory of the efficacy and/or safety of the 2 drug. 3 MS. DILLEY: That's public information? 4 DR. CARPENTER: That's public information, 5 all those. I don't know whether every aspect of 6 end-of-phase-2 conferences is because those might 7 be protected by trade secrets. So there is often, 8 by the way -- there is an exception to the Freedom 9 of Information Act, whereby certain features of a 10 not-yet-approved drug product are not available for 11 the public. But that's a whole separate area of 12 law. 13 But I just want to emphasize that none of 14 that prevents the FDA in the pharmaceutical world 15 from asking for more data later on, saying that the 16 conduct of the study or that the study, once 17 completed, even though we thought the protocol was 18 fine at the time, raises more questions than in 19 answers, and as pharmaceutical companies and all 20 sorts of people will be happy to tell you, reject 21 repeatedly and delay repeatedly -- and I'm not 22 saying for good or bad reasons. I think, quite</p>
<p style="text-align: right;">Page 110</p> <p>1 of institutions, has had some over the past 50 to 2 60 years -- thank you for saying my book; I'll 3 donate the -- 4 MR. MYERS: I recommend everybody in the 5 room read your book, so that's all right. 6 DR. CARPENTER: -- but where it's had it, 7 and so we're concerned about this. But let me just 8 be very clear that at some level, again, the FDA 9 does a good bit of this. 10 Now, third-party institutions, specifically 11 no, but if I just look at the pharmaceutical world, 12 initial approval of protocols, essentially, CDER 13 does that, if not with a wink and a nod, in 14 pre-phase 1, pre-phase 2 meetings. Approval of 15 protocols for phase 3 clinical trials at end of 16 phase 2 conferences, they do it already. 17 And any time, essentially, the FDA lets an 18 IND, which is an investigational new drug 19 application, run out into the market without 20 halting it later, they are giving their implicit 21 sanction to at least the study design as 22 potentially indicative of -- or as potentially</p>	<p style="text-align: right;">Page 112</p> <p>1 possibly, the public health is served by these 2 decisions later on. 3 So I'm a little doubtful of the claim that 4 by just giving a thumbs up to the go-ahead with a 5 third-party study, the FDA is somehow committing 6 itself to approving the product. 7 The experience we have from 50 to 60 years 8 of pharmaceutical regulation, in fact, if anything, 9 the opposite occurs, much often to the 10 consternation of the industry in that field. Maybe 11 this industry is different, but I just want to put 12 that out there, that I don't see a hard link 13 between those two. 14 MR. MYERS: I see what you're saying, then. 15 A couple of distinctions that I think are 16 important, one of which is, we explicitly endorse 17 the idea of FDA spending a great deal of energy in 18 coming up with their recommendations about study 19 design and the like with regard to that. We think 20 that's absolutely fundamental, more fundamental 21 here even than with the pharmaceutical industry 22 because we've just seen repeated examples of the</p>

<p style="text-align: right;">Page 113</p> <p>1 industry producing science designed to show that 2 its products don't cause harm or that particular 3 additives don't cause harm, which subsequent 4 independent review after publication has 5 demonstrated that the science was flawed, and 6 probably intentionally flawed to be honest with 7 you. 8 So that sort of activity is something that I 9 think we're supportive of and is more necessary 10 here, I think, than it is even with the 11 pharmaceutical industry because of the abuse that 12 the industry has done up to this point in time. 13 What we object to is pre-approving not study 14 design but entities that would be deemed to be in 15 advance credible because of the history in this 16 case of a willingness to abuse institutions. And 17 I'm not actually critical of the institutions 18 because I think they got taken by an unscrupulous 19 industry, because they operated with innocence and 20 belief in the scientific process. 21 DR. CARPENTER: That's naive. 22 MS. DILLEY: Obviously, it's a bigger topic</p>	<p style="text-align: right;">Page 115</p> <p>1 SRNT over 10 years ago, and that was one of my 2 first forays into the world of tobacco control, and 3 I've been hooked on it since then. So, hopefully, 4 that means the meeting was a success. And I was 5 also among the co-authors on the paper on tobacco 6 funding models that Joanna introduced. 7 But in my remarks here, I want to address a 8 couple of other elements of this issue. First, is 9 to just point out some lessons from history that I 10 think are important to remember, to understand the 11 nature of the distrust that exists around tobacco 12 industry funding of research and also involvement 13 with the research community and, secondly, to show 14 how the lack of trust really goes beyond the 15 conventional concerns we have maybe in other areas 16 of biomedical research around potential conflicts 17 of interest. So they are, therefore, maybe 18 requiring special attention. 19 So, in particular, the concern here is not 20 just about the validity and integrity of research 21 results -- which is often our concern when we talk 22 about scientific integrity, we're concerned about</p>
<p style="text-align: right;">Page 114</p> <p>1 and you're not going to be here this afternoon in 2 Q&A. So I'm glad you raised it because it's 3 something that the rest of the panel can also 4 address. 5 I'm going to hold your question, Corinne, if 6 you can wait, because we've got two other 7 presenters. So Matt, thank you very much. 8 MR. MYERS: Sure. 9 (Applause.) 10 MS. DILLEY: Next, we have Mark 11 Parascandola, who is an epidemiologist in the 12 Division of Cancer Control and Population Sciences 13 at the National Cancer Institute, National 14 Institutes of Health, and Dr. Parascandola will be 15 giving this presentation now. And then also, after 16 the model presentations this afternoon, we'll help 17 start up the conversation around translation into 18 the tobacco arena. So thank you very much for 19 doing double duty today. 20 Presentation -- Mark Parascandola 21 DR. PARASCANDOLA: Thanks. Good morning. 22 So I was also at that meeting in New Orleans around</p>	<p style="text-align: right;">Page 116</p> <p>1 biased results and this sort of thing -- but also 2 about the nature of the relationship between the 3 tobacco industry researchers and public health 4 authorities and how that relationship has sometimes 5 been misused. 6 So following the release of the 1964 7 report -- this is kind of the first episode I 8 wanted to bring up. Following the release of the 9 1964 the Surgeon General's report on smoking and 10 health and efforts to begin controlling cigarette 11 labeling and advertising, senior staff members of 12 the Tobacco Institute, which was at the time a 13 tobacco industry trade organization, went about 14 "seeking dialogue and scientific cooperation --" 15 those are their words -- with senior officials in 16 the Department of Health, Education, and Welfare. 17 And here is an excerpt from one of the internal 18 industry documents talking about this effort. But 19 according to their planning notes, the Tobacco 20 Institute intended to propose the creation of a 21 central agency for tobacco research with joint 22 oversight from government and industry, so that</p>

<p style="text-align: right;">Page 117</p> <p>1 both groups would -- and these are their words 2 again -- "speak with one set of figures." 3 As explained in their memo, one of the 4 motives for this effort was the understanding that 5 scientific cooperation between industry and 6 government, or at least the appearance of 7 cooperation, could diminish the basis for -- again, 8 their words -- "reckless and untimely regulatory 9 action." 10 Tobacco industry president Earle Clements 11 met with HEW's secretary at the time, John Gardner, 12 and then subsequently his successor, Wilbur Cohen, 13 a number of times from 1966 to 1969 to discuss 14 collaboration in this area. 15 So one of the things that came out of this 16 effort was there was a joint committee on tobacco 17 and health that was established in 1968, including 18 representatives from the National Institutes of 19 Health, the industry-run Council for Tobacco 20 Research, and the American Medical Association's 21 program on tobacco and health, which was also 22 funded by the tobacco industry. And over a number</p>	<p style="text-align: right;">Page 119</p> <p>1 around what was called at the time less hazardous 2 cigarettes or potentially less hazardous 3 cigarettes. And the working group included 4 representatives from academia, government, and also 5 the tobacco industry. And I have highlighted in 6 red here three senior research officials from R.J. 7 Reynolds, Lorillard, and Philip Morris. And the 8 folks on here were among some of the longest- 9 running members on this panel. 10 This effort continued over a period of about 11 10 years, and I don't have time to go into all the 12 details here. But I wanted to point out that the 13 tobacco industry benefitted in several ways from 14 their participation in this effort. First of all, 15 they gathered information about developing public 16 health service research initiatives in thinking 17 around tobacco that was not otherwise public. 18 Industry representatives also sought to influence 19 the direction of research programs and discourage 20 research in certain areas. 21 They also gained an appearance of 22 cooperation with government officials and</p>
<p style="text-align: right;">Page 118</p> <p>1 of years, this committee met and discussed various 2 research needs and tried to develop a joint 3 statement. 4 They were unsuccessful in doing so because 5 they couldn't agree on the language. They couldn't 6 agree on background language to set up the 7 document. And, in particular, the Council for 8 Tobacco Research and AMA research program 9 representatives objected to language inserted by 10 NIH, which summarized the current state of 11 knowledge on smoking and health, based on the 12 Surgeon General's reports and other information. 13 So there was no document that came out of 14 this effort, but the tobacco industry did gain 15 positive publicity via public statements from 16 senior government officials highlighting the many 17 research gaps that still remained on smoking and 18 health and also highlighting this government 19 industry collaboration in the area. 20 The second episode I want to mention, at the 21 National Cancer Institute, starting in 1968, there 22 was a working group formed to begin to do research</p>	<p style="text-align: right;">Page 120</p> <p>1 benefitted from the semi-official endorsement of 2 the low-tar cigarette strategy. And at the same 3 time, industry representatives did not share much 4 critical information about their own research on 5 nicotine dependence and smoking behavior at the 6 time, which could have certainly been of direct 7 relevance to this effort. 8 Finally, the fact that the tobacco industry 9 was producing cigarettes with lower tar and 10 nicotine content at the time, as recommended by the 11 tobacco working group, may have helped to stave off 12 more rigorous regulation and control of tobacco 13 products during the 1970s. 14 So I think, in sum, the tobacco industry 15 really benefitted much more from this relationship 16 than the public health community did. 17 The second component here that I wanted to 18 address is how the concerns around trust in tobacco 19 industry-sponsored research are different from 20 those in thinking about other kinds of research 21 such as research funded by the pharmaceutical 22 industry. Formal attention to conflicts of</p>

<p style="text-align: right;">Page 121</p> <p>1 interest and research integrity are really 2 relatively recent. I think it's the increasing 3 commercialization of biomedical research in the 4 1980s that led to a lot of these policies that are 5 now ubiquitous in research institutions. 6 The concern at the time was that, under some 7 of the academic industry collaborations that were 8 developing with the growth of biomedical research 9 in the 1980s, and suddenly academic scientists and 10 institutions stood to gain financially, to a much 11 greater degree than ever before, from the 12 commercialization of research products. 13 So a number of universities and scientific 14 journals developed policies to address potential 15 conflicts of interest. And the primary mechanism 16 that's used is requiring disclosures, either annual 17 disclosures of outside activities, disclosure when 18 publishing a paper of sources of funding, and this 19 sort of thing. 20 Then in the following decade, during the 21 1990s, as litigation and investigation of the 22 tobacco industry progressed, there are a number of</p>	<p style="text-align: right;">Page 123</p> <p>1 So the tenor of these policies and their 2 intent really is very different. And in fact, in 3 1994, the National Cancer Advisory Board actually 4 included a recommendation in its report to Congress 5 proposing to withdraw federal funding from cancer 6 research organizations that accept tobacco industry 7 support. That never happens, but it shows you the 8 sort of level of concern there was about this issue 9 throughout the public health community and the 10 cancer research arena. 11 So these academic policies really single out 12 the tobacco industry as different from other 13 industries. They differ qualitatively from the 14 conflict of interest policies. And in addition to 15 their intent, most university conflict of interest 16 and research integrity policies include specific 17 mechanisms to require disclosure of measureable 18 financial interests or prevent particular types of 19 behavior by investigators, such as fabricating 20 data. And while these policies may have their 21 limitations and sometimes rely on voluntary 22 reporting, they are formalized and they utilize</p>
<p style="text-align: right;">Page 122</p> <p>1 academic institutions put into place, new policies 2 restricting acceptance or refusing acceptance of 3 tobacco industry funds. 4 But the content of these policies was very 5 different than the conflict of interest policies 6 that we saw from the previous decade. And instead 7 of focusing on concerns about bias or commercial 8 influence on interpretation of results, the 9 rationales really were stated more around the clash 10 of values and goals of industry versus the academic 11 institutions. 12 I've quoted from a few of these academic 13 policies on tobacco industry funding. And I point 14 out how the extent of disease, disability, and 15 death caused by smoking and the conduct of the 16 industry are so completely at variance with the 17 stated mission of the school: incompatibility with 18 the public health mission; any association with the 19 tobacco industry taints the reputation of the 20 college; tobacco companies produce a product and 21 have behaved in a manner that are at cross-purposes 22 to our academic mission.</p>	<p style="text-align: right;">Page 124</p> <p>1 standard enforcement and reporting procedures. 2 In contrast, these tobacco-specific funding 3 policies don't really cite specific mechanisms to 4 prevent bias or lack of objectivity in research. 5 They are comparatively informal. They don't cite 6 the fine mechanisms for enforcement, but really, 7 they focus on the unresolvable conflict of values 8 as their primary rationale. 9 So in some sense, their purpose is not so 10 much to regulate research or regulate the conduct 11 of research or how it's governed, but to really 12 make a public statement and put the institution on 13 record on this issue. And it's hard indeed to 14 imagine any circumstances under this sort of policy 15 under which a funding arrangement with the tobacco 16 industry would be acceptable. 17 So I just wanted to conclude with some 18 issues to consider, I think, going forward in 19 thinking about how we would handle third-party 20 governance of research funded by the tobacco 21 industry. So first is, I think it's important to 22 keep in mind who stands to gain from a particular</p>

<p style="text-align: right;">Page 125</p> <p>1 governance structure or arrangement. I think, as 2 we've seen here in the past, the tobacco industry 3 has gained far more than the public health 4 community from its involvement in public health 5 research programs. 6 Secondly, conflict of interest and research 7 integrity mechanisms are necessary but not 8 sufficient for addressing the concerns over 9 tobacco-industry funded research. Industry 10 involvement in the less hazardous cigarette program 11 was not a secret, but the industry representatives 12 were still able to have an adverse impact on that 13 research. 14 Third, I think it's important to be aware of 15 how a tobacco company or companies might use their 16 support of research or contractual arrangements 17 with an independent research institution in ways 18 adverse to public health, such as for PR purposes 19 or trying to use the independent authority of a 20 third-party organization to endorse a certain 21 approach to research or certain conclusions about 22 less hazardous products.</p>	<p style="text-align: right;">Page 127</p> <p>1 of addiction. This was, of course, at a time when 2 addiction, at least in the public health community, 3 was not well understood, so ensuring that kind of 4 diversity of disciplines is important, too. 5 Finally, I would say that there is a real 6 and potential danger in putting the FDA in the role 7 of approving certain research structures or 8 arrangements, as this creates exactly the kind of 9 semi-official stamp of approval on research 10 conclusions that can be potentially misused as in 11 the past. 12 So thanks. I'll stop there. 13 (Applause.) 14 MS. DILLEY: A couple of questions? Yes? 15 MR. ROSE: Hi, Jed Rose again. Mark, could 16 you elaborate a little bit on the term -- and in 17 previous talk as well -- the term the tobacco 18 industry has used as if it's a monolithic entity, 19 more of a monolithic entity that hasn't changed in 20 the last 50 years? 21 Just two examples to stimulate your 22 thoughts, whereas decades ago, everybody remembers</p>
<p style="text-align: right;">Page 126</p> <p>1 Fourth, it's important to think about who 2 defines the research agenda in question. So our 3 concern is not just with making sure that research 4 is conducted in a way that preserves scientific 5 integrity, but also thinking about who decides what 6 are the key research questions and who is involved 7 in that process. Certainly, I think it was, in the 8 case of the less hazardous cigarette program, not 9 beneficial to have industry representatives 10 involved in that role. 11 In addition to the concerns about the need 12 for independence and transparency, I would add that 13 diversity of disciplines is important, too. This 14 is another lesson that came out of understanding 15 the history of research on low-tar, and light 16 cigarettes, and the less hazardous cigarette effort 17 at the NCI. 18 Because the research program was defined 19 very narrowly, it was more vulnerable to being 20 misled. And so, for example, there was no research 21 being conducted under the NCI less hazardous 22 cigarette program on smoking behavior or mechanisms</p>	<p style="text-align: right;">Page 128</p> <p>1 the image of tobacco company CEOs saying, "Nicotine 2 and tobacco is not addictive," and so forth. And 3 now, some companies explicitly state that smoking 4 is harmful and causes addiction. Some companies 5 have engaged in ethical funding of research. 6 Also, if, for example, a deregulation were 7 to go into effect that classifies e-cigarettes as 8 tobacco products, then there is suddenly going to 9 be created a raft of companies which will now be 10 part of the tobacco industry. 11 So I guess what I'm suggesting is there's 12 tremendous heterogeneity within the present and 13 probably future tobacco industry. So to continue 14 using the label "the tobacco industry" doesn't seem 15 to be accurate anymore. And while we should all 16 remember the past and learn from it, what do you 17 think about how do you learn about the evolving 18 future of companies that may be making products 19 virtually indistinguishable from NRT? 20 DR. PARASCANDOLA: Yes. I think that's an 21 important point. I used the term tobacco industry 22 here in part because I was talking about an</p>

<p style="text-align: right;">Page 129</p> <p>1 organized strategy that was being put forward 2 through the Tobacco Institute, which was 3 representing the leading tobacco companies at the 4 time. So I think it's fair to call that 5 organization representative of the tobacco 6 industry.</p> <p>7 So in the episodes I'm talking about during 8 the '60s and '70s, when research was being 9 conducted on low-tar and light cigarettes, I think 10 it's very accurate to refer to the tobacco industry 11 in this combined sense.</p> <p>12 I wanted to draw some lessons that are still 13 relevant I think today. What we can learn from the 14 past is that even if the Tobacco Institute no 15 longer exists, some of the same strategies that had 16 been used by tobacco companies and the tobacco 17 industry as a whole are still of concern today. So 18 I think the lessons still apply, whether we're 19 talking about the tobacco industry as a whole or 20 certain individual companies.</p> <p>21 So, yes. I think that was the point I 22 wanted to get across here.</p>	<p style="text-align: right;">Page 131</p> <p>1 perspective. I'm in the trenches, so to speak, and 2 so I'm going to take a practical perspective on 3 this question. I feel like much of the discussion 4 so far this morning is -- and it's appropriate, but 5 is at a very high level. To some extent, the 6 details are going to matter most here. And so I'm 7 going to spend a little bit of time on those.</p> <p>8 So my perspective on this issue that we're 9 discussing today is that the current situation in 10 which the most addictive and deadly project is also 11 the most widely used is entirely unacceptable. And 12 I've been in this field, believe it or not, for 13 over 20 years, and I find it appalling, to some 14 extent, that we still have this conversation.</p> <p>15 So with that background, I also view the 16 Tobacco Control Act as giving the FDA the power to 17 effect important changes with the potential to 18 greatly reduce the death and disease caused by 19 tobacco. This potential, however, cannot be 20 realized without the active participation of 21 researchers like myself. And I'm speaking today 22 with my own opinion. I'm not trying to represent</p>
<p style="text-align: right;">Page 130</p> <p>1 MS. DILLEY: Other questions? 2 (No response.)</p> <p>3 MS. DILLEY: Great. You'll be back up for 4 the Q&A after lunch. So thank you very much.</p> <p>5 Next, the last presenter for this panel is 6 Eric Donny, who is an associate professor of 7 psychology and psychiatry at the University of 8 Pittsburgh.</p> <p>9 Presentation – Eric Donny</p> <p>10 DR. DONNY: Good morning. So by way of 11 background, I'm a researcher that does work on 12 nicotine, the role of nicotine and other 13 constituents, and drug-associated stimuli on 14 reinforcement and dependence. I am particularly 15 interested in how those mechanisms lead to the 16 consequent harm of cigarettes. This work is an 17 NIH-funded project, and the goal of that center 18 being to determine how market reduction in the 19 nicotine content of cigarettes might be used to 20 impact public health and to improve the health of 21 current cigarette smokers.</p> <p>22 So I come to this from a very practical</p>	<p style="text-align: right;">Page 132</p> <p>1 all researchers. But certainly I think some of the 2 issues I'll talk about today are those that would 3 be held by other colleagues.</p> <p>4 So whatever systems develop for assessing 5 modified-risk tobacco products, researchers have to 6 buy into that system. If they don't participate, 7 it won't work, and there will be no action taken 8 for modified-risk tobacco products, and 9 potentially, continued harm will persist.</p> <p>10 So hence, the priority for me and, I hope, 11 for CTP, is to find a way to get this research done 12 and to do so in the most efficient manner possible. 13 Regulation invariably slows progress, and that's 14 okay here. I mean, it's a necessary evil for many 15 of the reasons that have been talked about today. 16 However, unnecessary barriers and inefficiencies in 17 a system of products that could truly be modified 18 risk and therefore could improve the health of 19 thousands of Americans, have to be overcome.</p> <p>20 So this research has to be independent, but 21 it also has to be unbiased, and robust, and able to 22 withstand scrutiny to allow FDA to act swiftly.</p>

<p style="text-align: right;">Page 133</p> <p>1 So although our focus today is modified-risk 2 tobacco products, I think we need to be cognizant 3 that there's really two types of research related 4 to products that could be impacted by this model. 5 And this was alluded to a little bit earlier. 6 I want to keep the focus on modified-risk 7 products, but the other path for reducing the death 8 and disease caused by cigarettes is through product 9 standards. And it's unclear to me whether or not a 10 third-party governance model might have some 11 influence over this process as well. So I think 12 it's important that we keep in mind this other 13 process. 14 So from a practical perspective, what do 15 researchers need? What do we need to do? What do 16 we need to have in place to do our work? And 17 here's just a list of a few of the things I'm going 18 to cover. 19 So starting with funding -- I don't want to 20 spend much time on this. I think it's pretty 21 clearly articulated in the IOM report, and also, I 22 think it's something that we probably largely agree</p>	<p style="text-align: right;">Page 135</p> <p>1 scientific standards aren't clear yet, and so the 2 engagement of academic institutions is going to be 3 important. 4 In many ways, when I think about the role of 5 the industry -- and I'll use that loosely -- in 6 such a process, I think that it's really in some 7 ways as simple as providing the product, providing 8 the product claims, and the required or requested 9 information about that product to facilitate the 10 independent evaluation of the product. 11 The third party or the FDA should facilitate 12 appropriate disclosure about the product and be 13 able to evaluate the potential impact of the 14 product constituents and the design characteristics 15 in a way that guides research. 16 Compared to medications, tobacco products 17 are incredibly complex, with hundreds of 18 constituents and design features that could impact 19 their use and, ultimately, their effect on the 20 user. 21 So the FDA needs to err on the side of 22 transparency about products, which may come into</p>
<p style="text-align: right;">Page 134</p> <p>1 on. But to state the obvious, any funding 2 associated with modified-risk products cannot be 3 from the tobacco industry, and institutions have to 4 be assured -- and Joanna touched on this -- that 5 all contracts and grants given to researchers at 6 their institutions are free to report the data and 7 they interpret those data regardless of the 8 outcome. That has to be the starting point. 9 I'll talk a little bit more about this in a 10 bit, but that assumes that academic institutions 11 are actually the place where this testing occurs. 12 Another model and one that certainly could emerge 13 over time is when it's done through contract 14 research organizations. And so the concerns would 15 be different for CROs than they would necessarily 16 for academic institutions. 17 I personally think that academic 18 institutions, especially at this point in the 19 development of the science of modified-risk 20 products, are going to play a critical role. Maybe 21 someday in the future, CROs will be able to have 22 the expertise to conduct the work. But the</p>	<p style="text-align: right;">Page 136</p> <p>1 conflict with proprietary information that the 2 companies want to protect. However, given the 3 history of tobacco products in this country, I 4 think transparency has to win over proprietary 5 information. 6 Like medication trials, we need appropriate 7 control and comparison products. This isn't 8 obvious how this is going to be done. What is the 9 proper comparison for a modified-risk tobacco 10 product? The identification of design decisions 11 like that is going to need to involve academic 12 researchers. 13 We'll also need to likely navigate -- and I 14 know this through firsthand experience -- a 15 regulatory environment, investigational product 16 use. And this is one of those parts of the system 17 that could be, if we don't address it directly, an 18 inefficiency that could lead to continued use of 19 more dangerous products instead of less dangerous 20 ones. 21 Relatedly, I also believe we need a full 22 description of the known risks from hopefully some</p>

<p style="text-align: right;">Page 137</p> <p>1 sort of adverse event tracking system. And this 2 is, I guess, where I imagine a more unifying third 3 party system, not a bunch of splinter systems that 4 actually serve as a fast way for an industry, a 5 particular product to get approved, but a broader 6 adverse event tracking system so that we can 7 understand the relative risks of products. And 8 that can only be done through such a system that we 9 all utilize.</p> <p>10 Finally, again, from a very practical 11 perspective, as a researcher who has to go to my 12 IRB and say, "Here's a product I want to study," I 13 need an entity. I need some standards to educate 14 my IRB so that I can go about this research with 15 the highest degree of integrity, but also with some 16 efficiency, that I don't get bogged down in a 17 process that I can't communicate to my IRB, and 18 therefore can't study products that I think might 19 actually have some potential use.</p> <p>20 A critical issue that I'm also not clear 21 about is what methods or measures will be used to 22 evaluate products or even whether a standardized</p>	<p style="text-align: right;">Page 139</p> <p>1 imagine a third-party system doing. I can imagine, 2 for example, that the entity could reduce the 3 burden of addressing some of those regulatory 4 hurdles. They could facilitate some of the 5 challenges related to the product, things related 6 to the storage, distribution, blinding of product, 7 the choice of comparison products; that we don't 8 want the industry making those decisions because 9 they're critical design decisions that will 10 ultimately impact the interpretation of the data, 11 and the independence of this entity and the 12 researchers will be paramount.</p> <p>13 They even can support things like a 14 biomarker analysis or something that allows 15 researchers to do the things that will prove 16 critical in the evaluation of a product.</p> <p>17 Relatedly, the third party could provide 18 needed services related to ensuring the quality of 19 the research, study monitoring, and standard for 20 drug development. And I know it's mentioned in the 21 IOM report, or at least quality assurance is. But 22 to date, the FDA has no clear policy about the</p>
<p style="text-align: right;">Page 138</p> <p>1 approach is actually feasible at this point. If it 2 is the case that the design and data required by 3 the FDA are largely prescribed, then the role of an 4 academic researcher will be diminished, and they 5 won't engage in the process because their 6 institution won't look fondly on that kind of 7 contract research. Indeed, most institutions would 8 have little to do with that sort of process.</p> <p>9 So that said, I can imagine the FDA 10 considering evidence from a wide range of methods 11 and measures, some of which are shown here. My 12 personal opinion is that the evaluation of 13 modified-risk tobacco products is so new that 14 standardization is many years away and will be a 15 difficult process to describe.</p> <p>16 If that proves true, then, again, the 17 expertise of academic researchers on what design 18 and methods need to be utilized and how to properly 19 evaluate a product will prove critical. It is in 20 those details that the honesty of research is best 21 expressed.</p> <p>22 There are other tangible things that I can</p>	<p style="text-align: right;">Page 140</p> <p>1 requirements for clinical trials and the need for 2 study monitoring. And as someone who is in the 3 trenches, I can tell you that I think study 4 monitoring, independent of the researcher and the 5 industry, is going to prove critically important.</p> <p>6 Finally, this can't be emphasized enough. 7 Given the deep distrust that we've heard about this 8 morning and that many people have written about, 9 industry and industry-sponsored products have to be 10 evaluated by independent investigators. Any model 11 we consider cannot infringe upon that independence; 12 hence my idea that in some ways, it's relatively 13 simple. Provide us the product and nothing else, 14 information about the product, and let the 15 researchers figure out whether those claims are 16 justified or not.</p> <p>17 So in sum, I think the third-party system 18 must serve three things. It must facilitate the 19 researchers' ability to conduct the needed research 20 in an efficient and timely manner. Too many people 21 continue to use the most deadly product and each 22 day of unneeded delay literally costs lives.</p>

<p style="text-align: right;">Page 141</p> <p>1 The system must of course ensure the quality 2 of research procedures and data. It must have 3 checks and balances such as the close monitoring of 4 trials. And finally, the system must protect the 5 researchers' integrity and independence. Without 6 this, it will fail in facilitating the goal of the 7 actual act, which is to improve public health. And 8 that's it. 9 (Applause.) 10 MS. DILLEY: We have some time for a couple 11 of questions. Yes? 12 DR. PETERSON: Nice presentation. Eric 13 Peterson. Duke University. Just curious. Who 14 provides the funding under your model for those 15 researchers to carry out the research? 16 DR. DONNY: Yes. So are you asking whether 17 it is partly provided by public and partly provided 18 by private or the entity itself? 19 DR. PETERSON: I just didn't hear. 20 DR. DONNY: So from my perspective as a 21 researcher, the funding would have to come from an 22 entity that is separate from the industry. So if</p>	<p style="text-align: right;">Page 143</p> <p>1 Of course, this goes back to the standard in 2 911(g)(1), which is a public health standard, and 3 marketing and how the product interacts in the 4 marketplace will be critical. 5 DR. DONNY: Yes. So I couldn't agree more. 6 And I think that, ultimately, that's the standard 7 by which all products have to be evaluated, is are 8 they more likely than not to provide an increase in 9 the public health, to improve public health? 10 So I don't disagree with that at all. So I 11 don't want to say a priori that any particular 12 product or any set of products is likely to do 13 that. I simply think that we need to ask that 14 question of all products that are submitted because 15 it is certainly possible that some will. 16 If that's the case, we need to keep that in 17 mind. We need a true evaluation of that and an 18 efficient one because, in that way, lives are at 19 stake. If you imagine a product that actually 20 could improve the public health, then it seems to 21 me that we have to have a path to get there. 22 MS. DILLEY: Another question? Ay other</p>
<p style="text-align: right;">Page 142</p> <p>1 that third-party entity, for example, grants or 2 contracts, that the institution can recognize as 3 independent of the industry's goals, then I think 4 that's an okay system. 5 MS. DILLEY: Other questions for Eric? 6 MR. DOBBINS: I just want to issue -- and 7 this may be just a bit of a challenge. But I think 8 Matt made the point earlier -- and it's one I 9 concur with -- it certainly is clear that you can 10 make a nicotine delivery product that's less 11 hazardous than a cigarette in what probably is the 12 lowest consumer safety bar you can conceive for 13 anything. But it's not clear to me, as you say, 14 that lives are at stake, that the creation and 15 entry of that product into a commercial marketplace 16 where the cigarette is ubiquitous, billions and 17 billions of dollars a year are spent promoting it, 18 and it's sold by an industry that has demonstrated 19 an unceasing dedication to protecting its market 20 share in the cigarette, really that there are lives 21 at stake, as you say. And I wonder why you draw 22 that conclusion.</p>	<p style="text-align: right;">Page 144</p> <p>1 questions for Eric? Please introduce yourself. 2 MR. GRAFF: My name is Don Graff. I work 3 for Celerion. So as someone else who works in the 4 trenches, I really appreciate your presentation. I 5 want to touch on a question, a previous question 6 here, with regard to funding of a third-party 7 entity under your model. Where would that funding 8 ultimately come from? 9 DR. DONNY: I'm not sure I honestly have an 10 opinion about that, except for to say that, as a 11 researcher, that any funding provided by industry 12 would have to not infringe on the independent 13 evaluation of the product. 14 So that's the link that has to be broken and 15 broken with much clarity because researchers are 16 very trepidatious about this. They are rightfully 17 scared to engage in this, and so am I. And so in 18 the end, I need to know that whatever source of 19 funding there is, it does not impact -- and my 20 institution will have to know it does not impact 21 anything that I do, my ability to publish the data, 22 and the conclusions that I make about that product.</p>

<p style="text-align: right;">Page 145</p> <p>1 MS. DILLEY: Thank you.</p> <p>2 So we have time for one more question. I'm</p> <p>3 going to break a little early.</p> <p>4 MS. LEE: Monica Lee from GTI. One question</p> <p>5 I think might be better for the agency is, when we</p> <p>6 talk about research, there's a type of research</p> <p>7 which would come into a variety of tobacco</p> <p>8 products, working on the study designs, or you</p> <p>9 talked about method and measure. I think it's very</p> <p>10 important, because right now, we do not have that</p> <p>11 kind of information. There are also studies, or</p> <p>12 testings, or research specific to a potential MRTP</p> <p>13 candidate.</p> <p>14 So I think as we talk about conduct, it</p> <p>15 seems like a lot of discussion is geared toward the</p> <p>16 common type of studies, evidence which may not be</p> <p>17 tied to a specific product. But at the same time,</p> <p>18 and I think from the industry perspective, we also</p> <p>19 need to understand a particular product, how that</p> <p>20 goes through evidence that FDA may need.</p> <p>21 So when we talk about third-party</p> <p>22 governance, are we talking about type of study</p>	<p style="text-align: right;">Page 147</p> <p>1 of view. And I think that's part of the discussion</p> <p>2 that people are trying to raise, a variety of</p> <p>3 issues.</p> <p>4 So it's a good point. I mean, I think we</p> <p>5 haven't been rigorous about talking about one</p> <p>6 specific type of research, and, in fact, there are</p> <p>7 lots of different ways third-party governance could</p> <p>8 be applied. And that's I think part of the</p> <p>9 discussion, part of the issues that people have</p> <p>10 raised, and part of what CTP wants to hear more</p> <p>11 about in terms of providing input and perspectives.</p> <p>12 So with that, I want to thank you again,</p> <p>13 Eric, for your presentation.</p> <p>14 (Applause.)</p> <p>15 MS. DILLEY: Just a reminder about logistics</p> <p>16 for this afternoon, one is that we're breaking</p> <p>17 about 15 minutes early, so you have an hour and</p> <p>18 15 minutes, which is good because you have to go</p> <p>19 hunt and gather for yourselves on food. So I'll</p> <p>20 give you a little bit more time. There are, again,</p> <p>21 recommendations, a book out on a table out there.</p> <p>22 Then we will start right back up at 1:00</p>
<p style="text-align: right;">Page 146</p> <p>1 designs, structures, evidence-based applicable to</p> <p>2 all MRTPs, which is big research, or are we here to</p> <p>3 talk about a product, somebody has an idea, and</p> <p>4 might have a potential for MRTP, and there are</p> <p>5 steps that we know we have to go through, for</p> <p>6 example, through draft guidance, that came out a</p> <p>7 year ago?</p> <p>8 MS. DILLEY: I'm not sure that was a</p> <p>9 particular question to you, Eric, but I think your</p> <p>10 point is -- and several speakers have talked to</p> <p>11 some portion of that -- there is different kinds of</p> <p>12 research, whether it's specific, as you said, to an</p> <p>13 application, whether it's broadly applied to MRTPs,</p> <p>14 or it's even broader than that; and what are we</p> <p>15 talking about? What governance structures are</p> <p>16 situated for what types of research, how that</p> <p>17 governance structure operates, who comprises it,</p> <p>18 how it's funded.</p> <p>19 I mean, there are lots of different</p> <p>20 dimensions that people put on the table in terms of</p> <p>21 what -- or some constellation of traits that are</p> <p>22 either more or less acceptable from people's point</p>	<p style="text-align: right;">Page 148</p> <p>1 with the Q&A from this morning's panel. So we'll</p> <p>2 start that at 1:00. That'll be an hour and then</p> <p>3 we'll go into some of the presentations around the</p> <p>4 models. So thank you, and we'll see you in an hour</p> <p>5 and 15 minutes.</p> <p>6 (Whereupon, at 11:43 a.m., a luncheon recess</p> <p>7 was taken.)</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>

<p style="text-align: right;">Page 149</p> <p>1 AFTERNOON SESSION</p> <p>2 (1:01 p.m.)</p> <p>3 Q&A Session – Abby Dilley</p> <p>4 MS. DILLEY: Good afternoon. We're going to</p> <p>5 get started. And as you know from your agenda,</p> <p>6 we're coming back to the panel this morning.</p> <p>7 Daniel Carpenter had to leave, which is why we had</p> <p>8 a little bit longer Q&A period for him, but he had</p> <p>9 to catch a flight to Paris, poor guy. Yes.</p> <p>10 So he had to leave around lunchtime, but we</p> <p>11 do have all the members of the panel who spoke</p> <p>12 prior to lunch up here to address questions. And</p> <p>13 we will take questions from the audience. And if</p> <p>14 there are some submitted via e-mail, again, we</p> <p>15 encourage those of you who are attending online to</p> <p>16 do so.</p> <p>17 We're going to make a slight adjustment to</p> <p>18 this afternoon's schedule, per the presenter's</p> <p>19 request, which is, after the Q&A session for this</p> <p>20 morning's panelists, we'll take just a short break,</p> <p>21 maybe do our 15-minute break then, and then come</p> <p>22 back for the full panel discussion of the models</p>	<p style="text-align: right;">Page 151</p> <p>1 number of different ways.</p> <p>2 So the question tonight for the panelists,</p> <p>3 just to get your thoughts on this, is if GSK were</p> <p>4 to make and get approved a nicotine device using</p> <p>5 organically grown nicotine, but approved through</p> <p>6 the Centers for Tobacco Products as a modified-risk</p> <p>7 tobacco product, would GSK be a tobacco company?</p> <p>8 If not, why not? And then also, conversely</p> <p>9 with their existing line of nicotine replacement</p> <p>10 therapy products, although approved through</p> <p>11 CDER -- and I appreciate the very different</p> <p>12 regulatory mechanism -- is GSK a tobacco company?</p> <p>13 And again, if not, why not?</p> <p>14 MS. DILLEY: So part of your question, I</p> <p>15 think, is linking it back to its relevance for the</p> <p>16 viability of the third-party governance structure.</p> <p>17 And so the question is who governs or what role</p> <p>18 they might have as part of industry.</p> <p>19 Is that what you're asking? So anyone want</p> <p>20 to start? David, yes.</p> <p>21 MR. DOBBINS: I have a quick response. I</p> <p>22 think when you hear people like us, or you hear</p>
<p style="text-align: right;">Page 150</p> <p>1 from other arenas.</p> <p>2 So Richard Kuntz and Eric Peterson will be</p> <p>3 here to talk about those models. And then Mark</p> <p>4 Parascandola, who had been part of the morning's</p> <p>5 panel, will start trying to draw from those</p> <p>6 experiences and applying them to tobacco and some</p> <p>7 of the issues that were raised today. So a little</p> <p>8 translation of some of that, and some observations,</p> <p>9 and then also have a Q&A session this afternoon for</p> <p>10 those panelists to talk about the models.</p> <p>11 So with that, I will open it up to the group</p> <p>12 for questions for this morning's panelists. You</p> <p>13 also can ask questions of one another if you would</p> <p>14 like, and we'll get started.</p> <p>15 MR. HUFFORD: I'm Michael Hufford from</p> <p>16 eNicotine Technology. I thought it was a wonderful</p> <p>17 session this morning. Thank you. One question I</p> <p>18 had was about the evolving nature of this</p> <p>19 marketplace and what it means to be a tobacco</p> <p>20 company, maybe not today, but maybe five years from</p> <p>21 now, when the modified-risk tobacco product</p> <p>22 guidance is really off and running, perhaps in a</p>	<p style="text-align: right;">Page 152</p> <p>1 me -- I won't speak for everyone else -- say the</p> <p>2 tobacco industry, what we're really talking about</p> <p>3 is the industry that's selling deadly tobacco</p> <p>4 products like cigarettes and high-nitrosamine oral</p> <p>5 tobacco.</p> <p>6 The reason I think you see public health</p> <p>7 looking at scants of those companies is it's</p> <p>8 impossible to separate their motivations to obtain</p> <p>9 market share in those deadly products from their</p> <p>10 motivations to sell these other products that</p> <p>11 allegedly are going to show up in the market and</p> <p>12 make everybody healthy.</p> <p>13 The difference with GSK is the product</p> <p>14 they're selling isn't deadly, and it's designed for</p> <p>15 a specific therapeutic purpose. And it doesn't</p> <p>16 face those kind of competing incentives.</p> <p>17 So I think what you're hearing when I say</p> <p>18 tobacco industry, I'm thinking really about</p> <p>19 cigarettes and high-nitrosamine oral.</p> <p>20 MS. DILLEY: Other comments for the panel?</p> <p>21 MR. MYERS: It's a more complicated question</p> <p>22 because of the position taken by the electronic</p>

<p style="text-align: right;">Page 153</p> <p>1 cigarette industry, which was the industry that 2 claimed it was selling a tobacco product. And 3 therefore, it framed from a legal standpoint which 4 category it fell into. It had the opportunity 5 during the evolution of this legislation to be 6 treated differently and to be considered 7 differently. And instead what it chose was first 8 to exempt itself from this legislation and then to 9 fight FDA's effort to treat it as a drug and 10 device.</p> <p>11 So in its effort to escape all regulation, 12 the electronic cigarette industry has resulted with 13 a judicial decision, whether we agree with it or 14 not, that now throws it into the category of being 15 a tobacco product. Now, does that make somebody 16 who manufactures it a member of the tobacco 17 industry? I'll leave that definition of game 18 playing to others to decide.</p> <p>19 I think what's more important is to take a 20 look -- ask the question about how it should be 21 regulated, what rules should apply to it, how they 22 should be applied, and whether they can be applied</p>	<p style="text-align: right;">Page 155</p> <p>1 the tobacco market, however that novel product is 2 categorized.</p> <p>3 MS. DILLEY: Joanna or Eric, you're good? 4 Okay.</p> <p>5 Other questions? We'll go back here and 6 then up here.</p> <p>7 MR. DELMAN: Farrell Delman, TMA. I agree 8 wholeheartedly on the issue of profitability. I 9 don't think anything is going to go anywhere in 10 terms of companies wanting to market products if 11 they can't make money. I think that's a given. 12 And I think, David, you're absolutely right. 13 Profitability is key.</p> <p>14 What may be less understood is the fact that 15 the Reynolds CEO, Delen, has said he makes twice 16 the profit on Camel Snus than he makes on Camel 17 cigarettes. He'd love to more Camel Snus. That's 18 low-nitrosamine Camel Snus. If he can get the can 19 down in price, he'd make even more. This is a 20 relatively low economy of scale right now in 21 production because they're not selling all that 22 much. But if they were to sell 50 times as much,</p>
<p style="text-align: right;">Page 154</p> <p>1 in such a way that produces a public health 2 benefit, doesn't just expand dual use of those 3 products combined with all of the other tobacco 4 products that we know kill, with regard to those 5 issues, which is the reason why I think many of us 6 were most concerned about how do we get them into 7 the discussion about how to be regulated and why it 8 is so truly unfortunate that their answer was, 9 "Don't regulate me at all."</p> <p>10 MS. DILLEY: Other comments, Eric, or Mark, 11 or Joanna, the question at hand? Is it a complex 12 question around how you define industry and what 13 that means in terms of governance of the products, 14 et cetera? And Matt identified it's a fairly 15 complicated question, but from your perspective.</p> <p>16 DR. PARASCANDOLA: I would just add that I 17 would agree with the comment that, really, the 18 issue that -- conflict of interest, I think, that's 19 the key thing here. If a company has a vested 20 interest in an existing tobacco product that they 21 already sell, I think we would view that company 22 differently than a company that is not currently in</p>	<p style="text-align: right;">Page 156</p> <p>1 he'd make even more. He'd be the happiest camper 2 around if everyone smoking Camel cigarettes moved 3 to Camel Snus, and that's just the dynamic. That's 4 where the profits are for him.</p> <p>5 Now, I deal a lot with the new e-cig guys 6 out there, giving them advice on markets and things 7 like that. And my understanding in the e-cigarette 8 business, depending on how they source the liquids, 9 and the flavors, and the complexity there, buy that 10 is a very highly profitable business. That's why 11 we see so many of the players hitting the market 12 now, because even if they're selling small 13 quantities, they're making lots of money.</p> <p>14 Now, let's just say for the sake of 15 argument -- since profitability is absolutely key.</p> <p>16 MS. DILLEY: Is this to third-party 17 governance?</p> <p>18 MR. DELMAN: I want to get to David's point 19 and Mark's point about the connection between 20 profitability, because it's been raised, and any of 21 the issues associated with getting these products 22 out on the market through an MRTP governance</p>

<p style="text-align: right;">Page 157</p> <p>1 process, and what your thoughts are knowing that 2 they are profitable, and they'd be willing to give 3 up cigarettes. 4 MS. DILLEY: So I think your question is, 5 how much does profitability weigh into it in terms 6 of a governance structure? 7 MR. DELMAN: No, no. It's just, these 8 companies are willing to give up cigarettes if they 9 were able to promote and grow these other 10 businesses by virtue of being able to make 11 (inaudible -- off mic.) 12 MS. DILLEY: So you're asking about the 13 marketing regulations. 14 MR. DELMAN: Well, the process of getting 15 the relative-risk claim for a product that is -- 16 MS. DILLEY: I see. 17 MR. DELMAN: -- known to be less harmful. 18 MS. DILLEY: I see what you're saying. 19 I don't know if you've got a question in 20 there on third-party governance or if people 21 want -- 22 MR. MYERS: It's a hard one on third-party</p>	<p style="text-align: right;">Page 159</p> <p>1 exactly the goal you've wanted and to protect, if 2 there's such a thing, the honest manufacturer out 3 there from not having to compete against those who 4 are making either unsubstantiated claims or are 5 engaging in marketing that is really designed to 6 create dual use rather than single use. So the 7 statute creates all the incentives in the world for 8 what you want. 9 Now, in terms of the third-party 10 independent, this is in fact an area where my view 11 is not controlled by a sponsor or company, where if 12 FDA were funding research or if somebody else was 13 funding research carried out independently, so that 14 there was a way you could trust not just the 15 "product," but how the product was going to be 16 marketed and sold that it would produce that 17 result, then you would get -- and you've got 18 exactly the statutory system that would give you 19 what you want, and a truly independent party would 20 facilitate that. 21 MS. DILLEY: Any other comments along those 22 lines? David?</p>
<p style="text-align: right;">Page 158</p> <p>1 governance with regard to it -- 2 MS. DILLEY: Right. 3 MR. MYERS: -- except that Section 911 gives 4 FDA -- requires FDA to take into account broad 5 public health impact. So Farrell, if 6 hypothetically you were right -- I'm not sure I 7 agree with you about Camel, but that's a separate 8 question. The quotes I've seen from our Reynolds 9 CEO says the money is in combusted cigarettes. But 10 we don't have to debate that. That's not the 11 issue. 12 The statute mandates that FDA consider what 13 the broad impact of a product's claims will be so 14 that it's either an opportunity or a hurdle for the 15 tobacco company to demonstrate that if allowed to 16 make claims for, in your hypothetical, Camel Snus, 17 and you could really move a substantial number of 18 people off of cigarettes, not just during the eight 19 hours they can't work, then that's a powerful 20 component to be made. 21 In some respects, the statute has created 22 all the incentives in the world to accomplish</p>	<p style="text-align: right;">Page 160</p> <p>1 MR. DOBBINS: Matt, that's terrific and 2 that's a lot better than what I was going to say, 3 which is, the statute sets out the requirements for 4 the exact reasons you say, to make those claims. 5 But why it's relevant to third party -- is the real 6 key here -- is because the marketing of the product 7 will be critical in making the statutory claim. 8 So if you imagine a third-party entity that 9 says, "If the product looks this way, if it's 10 controlled this way, and if it's marketed this way, 11 it will positively impact the public health. Okay, 12 RJR. Go sell those next to your Camel cigarettes, 13 and we'll step back, and wait, and see if that 14 really happens," I think RJR has to show what it 15 will do. It has to make those claims, and it has 16 to be the one making scientific claims that can be 17 tested, replicated, and analyzed by publicly 18 available data. And that's one of the main reasons 19 Legacy opposes IOM Recommendation 10. 20 MS. DILLEY: So we have one brief follow-up 21 because we have a couple of other presenters. 22 MR. DELMAN: I would agree, Matt, that 911</p>

<p style="text-align: right;">Page 161</p> <p>1 sets out a whole range of requirements, and 2 standards, and issues. And obviously, any company 3 coming and making a claim is going to have meet 4 those hurdles. 5 What it does not do is answer what would be 6 a non-evidentiary, non-scientific claim, dealing 7 with what is indeed the calculus to evaluate 8 population risk. When you look at a product, the 9 new product coming on the market, the concern, 10 justifiably, is non-consumers of any nicotine 11 products at all being drawn to that product versus 12 the individual benefit that would come. 13 But what is that formula? What is that 14 calculus? What does it look like? Somebody is 15 going to try to meet that standard that is set out, 16 there and you don't know what the calculus is. How 17 could you possibly invest the money to try to 18 accomplish something so unknown? 19 MR. MYERS: Well, no, it's an interesting 20 question and it's an important question. The 21 statute sets out pretty clearly the criteria. The 22 details from which a formula would come shouldn't</p>	<p style="text-align: right;">Page 163</p> <p>1 says it's got to be careful. 2 MS. DILLEY: So okay. Mark, you want to 3 respond to that as well? 4 DR. PARASCANDOLA: Yes. I was going to add, 5 too, that I think in terms of that calculus for 6 evaluating risks and benefits, I mean, if you look 7 at the way the pharmaceutical industry has been 8 regulated by FDA, it has taken us a hundred years 9 to flesh out the requirements for evaluating the 10 risk-benefit calculus for pharmaceuticals, and it's 11 still evolving. 12 So I don't envision that necessarily an 13 agency would be expected to put in place, in a 14 short time frame, a detailed set of criteria for 15 meeting that calculus. I think it's likely 16 something that would evolve with input from the 17 scientific community and in ongoing research. 18 MS. DILLEY: So you think that clarity will 19 be developed over time as opposed to that being 20 some role that a third-party governance structure 21 could provide some insight to. 22 Matt, I think you raised that it could be</p>
<p style="text-align: right;">Page 162</p> <p>1 be in a statute and are, of necessity, not in this 2 statute. So between FDA, or between an independent 3 panel, or between TPSAC, there needs to be put meat 4 on those bones with regard to that. 5 I should say to you, perhaps ironically, if 6 the concerns you raise are in fact the concerns of 7 the broader industry, then the fact that a number 8 of manufacturers have challenged the very existence 9 of the public health standard as being 10 unconstitutional, and the fact that the industry 11 has given every impression that if FDA were to try 12 to put parameters on how it was marketed, that that 13 would be challenged under First Amendment purposes, 14 means that in some respects the industry has 15 already -- at least categories of the industry are 16 working against the exact goal that you're talking 17 about, because an agency, in order to carry out 18 that purpose, needs to know that it's working with 19 somebody, an entity, where it can have a role in 20 dictating not only the product itself, but how the 21 product is used. And if you can't be certain about 22 that, then the cautionary principal in the statute</p>	<p style="text-align: right;">Page 164</p> <p>1 TPSAC. It could be any number of ways that you 2 would go at that. 3 MR. MYERS: And that would be an interesting 4 use, broadly answering the question rather than in 5 regard to a specific thing, but to provide those 6 sorts of parameters and thinking on it. I think 7 you won't be surprised. I mean, those of us think 8 it should be done very much independent of the 9 industry so that there is no conflict, so that one 10 can be certain that the people chosen have only 11 reducing the death and disease caused by tobacco 12 products as their criteria. 13 MS. DILLEY: Right. And that's where it 14 sounds like from concerns raised earlier this 15 morning about it's not for a particular product, 16 but it's for a -- it's giving some clarity around 17 those standards, how to interpret those standards, 18 and what studies could meet those standards. 19 MR. MYERS: That would be my view. 20 MS. DILLEY: I know we had a question back 21 here. And please introduce yourself, if you would. 22 MR. WILLIAMS: Yes. I'm Linc Williams from</p>

<p style="text-align: right;">Page 165</p> <p>1 AEMSA. So there's been a lot of talk about lies 2 and deceits over the past multiple decades. So my 3 question to you is, there are now electronic 4 cigarette manufacturers, hundreds, if not thousands 5 of them, out there. Do you believe that they will 6 perpetrate the same lies and deceits that the 7 tobacco industry did in the last 20 to 30 years? 8 MS. DILLEY: And it's relevance for third- 9 party governance in terms of their participation? 10 MR. WILLIAMS: Because I believe -- should 11 the third-party governance also apply to the 12 electronic cigarettes? 13 MS. DILLEY: To e-cig. Okay. That was the 14 question. 15 MR. MYERS: I don't think it should depend 16 on anyone's beliefs. I think the purpose of giving 17 the FDA this sort of authority was so that we don't 18 have to depend upon that kind of faith. The FDA 19 should set up a set of rules and regulations that 20 apply across the board. It should be applied even- 21 handedly and rigorously, and that those who play by 22 the rules can benefit, and those who don't won't be</p>	<p style="text-align: right;">Page 167</p> <p>1 I heard discomfort around sort of just them 2 saying, "Harvard's a reputable institution. Duke's 3 a reputable institution. And the industry can fund 4 researchers from those types of institutions," and 5 that would be a pre-approved institution. 6 Then I heard what John was talking about was 7 more of an institution that's set up independently 8 and funded specifically for the purpose of doing 9 the grant-making almost in review process, 10 for -- for example, if a tobacco industry wanted to 11 sponsor a product, they could say they needed these 12 types of studies to meet the criteria, the MRTP. 13 And this other institution would then put out calls 14 for proposals, review them, and put out the grant 15 money. 16 So I guess I wanted to ask, especially Matt 17 and David or the folks who are saying no third- 18 party governance, are you opposed to all models, or 19 what do you see as the potential pitfalls of what 20 Joanna was specifically proposing? 21 MS. DILLEY: So Corinne, just so I 22 understand the question now, it seems to revolve</p>
<p style="text-align: right;">Page 166</p> <p>1 allowed to get away with it with regard to those 2 issues. 3 I think the one lesson of the last 50 years 4 is that until there is a regulatory agency 5 overseeing the actions of companies in this field, 6 that we shouldn't just assume that what they're 7 doing is in the public health's interest. 8 MS. DILLEY: So it's less of who's doing the 9 research, but it's more what kind of research 10 they're doing and meeting the same standards. 11 Corinne, you had a question? 12 MS. HUSTEN: Corinne Husten, FDA. I wanted 13 to ask a bit of a clarifying question because it 14 seemed like the perspectives of the various 15 presenters, in a way, depended on how they were 16 thinking about that term "pre-approved 17 institution." So I was hearing a lot of concern 18 about a pre-approved institution that, basically, a 19 company might set up as their independent 20 institution that they would run funding through, 21 that it might be good on the route of like CAR or 22 some of those.</p>	<p style="text-align: right;">Page 168</p> <p>1 particularly around the pre-approval concept and 2 then also what exactly that entity is reviewing or 3 governing. 4 MS. HUSTEN: Yes. Like I said, it seemed 5 like the different sort of perspectives, to some 6 extent, hinged on different sort of definitions of 7 what that pre-approved institution might be. And 8 so I was just curious of how one model was put out 9 there by John. I was just interested in hearing 10 what the other panelists thought about that model 11 specifically. 12 MR. DOBBINS: I think that there are two 13 questions being asked. And I'm going to set to the 14 side the issue of a third-party entity that does 15 this specific kind of product research for MRTPs. 16 But let's conceive of a situation where you wanted 17 to fund general research to understand the effects 18 of tobacco products, generally, and answer some of 19 these questions, like what are the criteria that 20 you would use to determine the public health 21 standard. 22 Well, one way you could do that is you could</p>

<p style="text-align: right;">Page 169</p> <p>1 set up a government regulatory agency, require the 2 tobacco companies to pay a certain part of their 3 money into that agency, and then empower the agency 4 to set up and fund studies that would address those 5 questions. But the good news is, we already did 6 that, and it's called the FDA, and they are doing 7 that stuff.</p> <p>8 So that, I am fully for. And I must say, 9 those of you who know who I am, I'm from Legacy. 10 And what happened is, the states sued the tobacco 11 industry for the costs incurred through industry 12 fraud that resulted in Medicaid expenditures. They 13 set aside a portion of that recovery from the 14 settlement to fund us. We do tobacco education. 15 And I can assure you that the tobacco industry has 16 no control over what we're doing.</p> <p>17 So there are models that you could do that 18 kind of general research on. The problem is when 19 you get into product-specific research and 20 particularly these kind of products, trying to 21 practically apply the model that I think is being 22 advocated here. It just breaks down when you try</p>	<p style="text-align: right;">Page 171</p> <p>1 quickly -- what I submitted looked at a number of 2 other instances where we've tried to do that. I 3 mean, Mark spoke about the NCI Tobacco Working 4 Group. When I was at the Federal Trade Commission, 5 we looked at the impact of the industry funding of 6 the American Medical Association, theoretically, to 7 do totally independent research.</p> <p>8 There was the Damon Runyon Foundation, which 9 was set up as theoretically a public institution 10 that was incorruptible to fund this sort of 11 research. And then, of course, you have the litany 12 of the universities that took tobacco money, only 13 some of which we take off this morning.</p> <p>14 Then, when you take a look at what they 15 produced, which you found was that the funding 16 controlled the agenda and moved the agenda away 17 from the things that would have a major public 18 impact, that much of the research itself was 19 research that the industry knew in advance would 20 either produce nothing or would run contrary to the 21 consensus that was out there. So that what the 22 lesson for me on those things is that the AMA and</p>
<p style="text-align: right;">Page 170</p> <p>1 to apply it in the real world.</p> <p>2 The FDA finds an entity, and I'll call it 3 Good Research, Inc. And Good Research, Inc., for 4 some reason, we can trust to do this product 5 research. So Good Research, Inc. takes the new 6 nicotine spray, and says it's great, and says, "If 7 you market it with these very specific 8 restrictions, we think they are great studies that 9 we've done ourselves, that would show that it would 10 reduce public health. Here you go, tobacco 11 industry. You can sell this right next to your 12 billions and billions of dollar market in 13 combustible cigarettes."</p> <p>14 Do you have any faith that those marketing 15 restrictions will hold up over time, that the 16 industry can be trusted to do the things that will 17 actually reduce that market? And the answer is, of 18 course you can't. So that's why it just doesn't 19 make any sense to us.</p> <p>20 MS. DILLEY: For product-specific? 21 MR. DOBBINS: Yes. Product-specific. 22 MR. MYERS: Corinne, let me just try to</p>	<p style="text-align: right;">Page 172</p> <p>1 NCI are extraordinary institutions, but the money 2 corrupted and the money created an agenda that 3 wasn't the appropriate agenda.</p> <p>4 If what you're talking about here is having 5 a third-party entity that isn't designed to help 6 company X move product Y to market, but is designed 7 to help the FDA say what kind of research do we 8 need to do to make sure that products in this 9 category are in fact less dangerous or that 10 marketing of this sort won't produce the results 11 that we're concerned about, that raises a very 12 different set of questions.</p> <p>13 But when Dan Carpenter presented this 14 morning, he started off by saying what they were 15 talking about. And he said, "We're flexible. It 16 isn't in the long term what we want. What we're 17 talking about is in fact a sponsor, company X, who 18 has product Y, who wants to move it through the 19 process, and therefore wants you to do research of 20 that sort alone."</p> <p>21 There's another question, too, which is, it 22 might not be inappropriate for some third party to</p>

<p style="text-align: right;">Page 173</p> <p>1 help the agency -- although I think TPSAC could do 2 this -- is, say, if somebody is producing a product 3 which they claim causes less cancer because it has 4 lower levels of nitrosamines in it, generically, 5 what kind of research do we need to do to be 6 comfortable with that, as opposed to in the context 7 of, I've got this product out here with regard to 8 it; something along those lines.</p> <p>9 But I think the second you get to that other 10 area, you've got a real problem. And I think the 11 notion that it's an independent entity, one needs 12 to be very cautious and skeptical. History just 13 tells us that there are real problems.</p> <p>14 MS. DILLEY: Joanna?</p> <p>15 DR. COHEN: So we have the FDA, and the Act, 16 and that's great, and it requires research to be 17 done on these products. And I think, as Eric 18 mentioned, a lot of scientists are very nervous 19 about taking money directly from tobacco companies. 20 And I think that's where -- whether this governance 21 structure, again, where there's one, would be 22 helpful to get the best people doing that possible</p>	<p style="text-align: right;">Page 175</p> <p>1 DR. PARASCANDOLA: Yes. I just wanted to 2 add, briefly, too, in response to Corinne's 3 question. So I think part of the concern with the 4 notion of -- or the term pre-approval is that the 5 concern is not just with organizations that have 6 been established by industry to support research 7 like the Council for Tobacco Research and that, but 8 also even how the tobacco industry has used the 9 reputation of NCI, of Harvard University, others to 10 sort of aid their corporate image and to provide a 11 semi-official support for their effort to market 12 low-tar cigarettes in the '70s. So that was the 13 historical example I had wanted to highlight.</p> <p>14 So even when we're talking about an 15 institution that is independent of the tobacco 16 industry, I think there are still concerns about 17 how the authority of that institution can be 18 misused.</p> <p>19 MS. HUSTEN: So I guess my question 20 is -- I'm sorry.</p> <p>21 MS. DILLEY: Can we have Eric speak to it? 22 And then we'll come back to you.</p>
<p style="text-align: right;">Page 174</p> <p>1 to do that research. Otherwise, what we're going 2 to end up with is the favorite people, contract 3 people, doing the research, and no one is going to 4 be able to trust. Their credibility throughout the 5 process is going to be lost.</p> <p>6 So I think we have to think about how we can 7 structure the money through a way, and whether FDA 8 is that third-party governance structure, meeting 9 some of the criteria that we laid out, that could 10 possibly be; we have to think that through. But I 11 think we want to be able to let our colleagues do 12 the good research that's needed in a way that their 13 reputations don't get tarnished and they can 14 continue to do that.</p> <p>15 So as I mentioned in my presentation, the 16 one challenge -- or the one criteria that we laid 17 out was the idea of an independent research agenda. 18 And that does completely fall apart when we're 19 talking about MRTPs because, obviously, the 20 research agenda is right there. So that one 21 certainly does fall apart.</p> <p>22 MS. DILLEY: Mark and then Eric.</p>	<p style="text-align: right;">Page 176</p> <p>1 DR. DONNY: Sure. So, I mean, I guess my 2 assumption is that the only model worth even 3 discussing is one in which the entity is probably 4 more like Joanna laid out, in that if we're talking 5 about a bunch of splinter entities that basically 6 serve the proxy function of being the industry's 7 representative, then of course that's not 8 independent research, and that's not viable, and 9 would not be acceptable to me or anyone else. So I 10 do think that it's more along those lines; at 11 least, that's my opinion.</p> <p>12 I think the part that Matt laid out, which I 13 think is where it gets more and more complex, is if 14 you lay out the marketing strategies now for those 15 products and you start to think about how are they 16 actually going to be used in the marketplace and 17 what are we testing in trials versus what are we 18 actually observing post-market in a surveillance 19 system where we think, oh, no, we got it wrong.</p> <p>20 I think that's where all the bias and lack 21 of independence is particularly problematic. And I 22 think that's where the FDA or CTP needs to provide</p>

<p style="text-align: right;">Page 177</p> <p>1 some guidance as to what exactly are the questions 2 that this entity and then the researchers who would 3 actually do the work, what exactly are the 4 questions that they're asking. What's the context 5 in which this product is being evaluated? 6 Otherwise, what I think we end up generating is 7 still research that's not relevant to what we're 8 trying to predict, which is how it functions in the 9 marketplace. 10 MS. DILLEY: And doesn't the statute speak 11 to that in terms of their requirements around 12 post-marketed surveillance and the ability of FDA 13 to pull from the market -- 14 DR. DONNY: Yes. 15 MS. DILLEY: -- so that we need those 16 anticipated public health benefits? 17 DR. DONNY: Yes. So my assumption is that 18 any third-party governance model will include both 19 pre-market and post-market surveillance in terms of 20 evaluating the product. Now, maybe that's wrong. 21 I mean, I think that was just my assumption coming 22 in. But I can't see how you can functionally</p>	<p style="text-align: right;">Page 179</p> <p>1 general -- 2 MS. DILLEY: -- like vulnerable populations 3 or -- but that's the example he used; what would 4 that look like. 5 MS. HUSTEN: Well, I heard a distinction 6 between general research on how you would do 7 studies from product-specific to bring a product to 8 market. So I guess my question is, how would you 9 set up a system to do the testing if someone wanted 10 to try to bring a product to market under an MRTP? 11 MS. DILLEY: Okay. And then Jed and Justine 12 back here. Anybody want to respond to that? 13 MR. MYERS: Three quick answers for you, I 14 think. As you struggle with the proper role here, 15 one is I think it's important for FDA to be setting 16 the agenda based on what it deems to be the most 17 important things and not to do it looking at 18 Section 911 in isolation with regard to that. 19 So in setting your priorities, I think the 20 agency needs to do that and determine with its own 21 funding research, and it has a very substantial 22 budget for research. Whether those dollars are</p>
<p style="text-align: right;">Page 178</p> <p>1 separate the two very effectively. 2 MS. DILLEY: Corinne, you wanted to follow 3 up? 4 MS. HUSTEN: Yes. I just wanted to follow 5 up a little bit, especially because what I was 6 hearing is like this set-up would be okay for more 7 generalized research but not for product-specific 8 research. 9 So setting aside whether you believe there 10 can be a modified-risk tobacco product or not, how 11 could someone potentially bring a product to the 12 testing to bring an application forward to FDA? If 13 the industry can't be trusted to do it themselves, 14 and if there's no third-party governance system 15 that will work, how can there be product-specific 16 research to even bring a product before FDA? 17 So I'm just curious how you would see a 18 system being developed that would allow for that 19 research. 20 MS. DILLEY: So Daniel gave a specific 21 example of -- 22 MS. HUSTEN: For a specific product, not the</p>	<p style="text-align: right;">Page 180</p> <p>1 best spent looking at those specific items or 2 whether they're spent looking at other items, I 3 don't want to prejudge that for you. 4 Second, ultimately, the agency is going to 5 have to evaluate whatever research done by whoever 6 it's done independently. So if I was going to tell 7 you what's your top priority -- my recommendation 8 for your top priority is, in fact, for the agency 9 to figure out what kind of studies it really needs, 10 with what kind of rigor and what kind of 11 methodology, so that it's not at the whim of the 12 industry or "some third party" who the industry is 13 dealing with. 14 Is that a challenge? Yes. But it was a 15 challenge for the FDA when they took on 16 pharmaceuticals, and it's a challenge when they 17 took on cosmetics, and it was a challenge -- it is. 18 And there's a learning curve because the industry 19 has hidden the information from us for all these 20 years, and so it's not surprising. 21 But I think that -- because ultimately the 22 agency has to make those determinations. From my</p>

<p style="text-align: right;">Page 181</p> <p>1 point of view, that's where the priority really 2 needs to be at the present time in setting your 3 priorities as to what you do with regard to this. 4 And that way, whether research comes in from a 5 tobacco company, from a university, or from some 6 other third party, you've got the criteria, you 7 have the in-house capacity to evaluate it, and 8 you're not dependent upon subcontracting that out 9 to somebody else. I mean, that was the reason for 10 having such a large budget for this agency, to give 11 it the capability of doing that moving forward. 12 MS. DILLEY: Mark, did you want to comment? 13 DR. PARASCANDOLA: Yes. So, yes, it's true. 14 Tobacco companies and especially a new company 15 that's maybe a smaller company may lack the 16 capacity now to do the kinds of studies that are 17 needed. But I wouldn't see them as somehow 18 disadvantaged because of that, because they have 19 the ability to develop the capacity that's -- or 20 they should be expected to develop the capacity 21 they need if they want to market that product. 22 So I guess, yes, I would agree with Matt</p>	<p style="text-align: right;">Page 183</p> <p>1 application. 2 DR. DONNY: Yes. When I think about the 3 history of the industry, that's what I would 4 emphasize, is there's really -- it's hard for me to 5 imagine any situation where I would be able to 6 trust the research being generated by an industry 7 that can turn profit based on that research. 8 That doesn't necessarily mean that profit is 9 a bad thing. I mean, obviously, as it's been said, 10 that's part of what will drive innovation. But in 11 the end, that research has to be able to withstand 12 an incredible amount of scrutiny from the public 13 health community, and that's appropriate. And I'm 14 not sure you can reach that goal any other way. 15 MS. DILLEY: So does that require a separate 16 verification process of researchers in an industry 17 or just they don't even do the research on a new 18 product at all? 19 DR. DONNY: I mean, this is where I think 20 there's a role for another entity or maybe it's 21 within the FDA. I don't know. But in the end, I 22 think what has to be done is there has to be an</p>
<p style="text-align: right;">Page 182</p> <p>1 that the focus really should be on looking at what 2 should the scientific criteria be to evaluate these 3 products and not primarily on how private companies 4 are going to develop the capacity to do that 5 research. 6 MS. DILLEY: Any other comments on this 7 particular question here? 8 DR. DONNY: I guess I just want to clarify 9 that. I would be personally uncomfortable -- and I 10 think based on scientific reasons -- to trust the 11 research that's generated by an industry that can 12 turn profit on that research. Now, that's in part 13 why I think ultimately this comes down to a test of 14 independence. The product has to be independently 15 evaluated. And what I mean by that is true 16 independence, separation of product and research. 17 So I think that that, to me, whether it's in 18 a third-party model or anything else, has to be the 19 criterion in which we develop infrastructure to 20 look at these products. 21 MS. DILLEY: So research is completely 22 separate from the industry that is making the</p>	<p style="text-align: right;">Page 184</p> <p>1 independent entity that actually determines whether 2 that research is of value or not. And that is in 3 the details. It's not just in the report. 4 MS. DILLEY: I believe, Jed, you were next 5 and then Justine. 6 MR. ROSE: Yes. Eric, you used the term and 7 others on the panel used the term that the history 8 of the industry or history of research supported by 9 the industry. I think it's important to remember 10 that, again, history evolves with time and there's 11 old history, recent history. 12 I think some of the recent history may be 13 relatively ignored in the discussions. Again, I 14 hold up the example when our institution accepted a 15 tobacco industry grant from Philip Morris U.S.A. 16 And the letter of agreement was posted on our 17 website, and the provisions of that public 18 transparent agreement involved no control by the 19 industry. Ownership of data, publication rights, 20 intellectual property all resided in the 21 university. 22 As you know, Eric, at any university these</p>

<p style="text-align: right;">Page 185</p> <p>1 days, all of the research we do, whether it's 2 tobacco industry-funded or NIH funded, is overseen 3 by a variety of committees within the university. 4 There is the Institutional Review Board that's been 5 spoken about often. There is the research 6 integrity office that requires conflict of interest 7 disclosures and can prohibit research where a 8 perceived conflict exists. There's a data safety 9 monitoring board in many cases, which we have with 10 our own center, which is another independent set of 11 people who can oversee side effects, and risks of 12 trials, and data management, data quality. 13 So there's already quite a few oversights 14 within any top-notch academic institution and more 15 coming all the time. I mean, there are new 16 committees being formed for new oversights all the 17 time. And so I just wonder how many -- and many 18 more oversight is needed for certain to protect 19 against specific concerns. 20 But I guess what I would invite you or ask, 21 why isn't there more interest in really delving 22 into learning about the current history of how</p>	<p style="text-align: right;">Page 187</p> <p>1 criteria. So, Eric, I don't know if you wanted to 2 answer, directed it to you, and anybody else can 3 chime in. 4 DR. DONNY: Sure, Jed. So I don't disagree 5 with many of the things that you said, that there 6 are -- and I certainly am sympathetic to the number 7 of regulatory things that we have to jump through 8 to prove that our work is of the highest integrity. 9 So I agree with that. 10 But I think the practical reality is that 11 whether you take recent history or a longer view of 12 history, the level of skepticism is incredibly 13 high, whether you think it's justified or not. And 14 without passing judgment on whether it's justified 15 or not, I think my colleagues would be happy to 16 probably contribute to that. But in the end, 17 practically speaking, I don't think the work moves 18 forward unless the system addresses that level of 19 skepticism. 20 So while I understand what you're saying, I 21 think that there is no way to assure the vast 22 majority of researchers of their independence and</p>
<p style="text-align: right;">Page 186</p> <p>1 things are done rather than focusing solely on the 2 relatively ancient history? In fact, anyone who 3 wants would have an open invitation to come and get 4 a seminar on what we have accomplished in terms of 5 advancing smoking cessation science with tobacco 6 funding that we've done, and what our oversight 7 mechanisms and mechanisms for protecting the 8 integrity of the research are. 9 So when you off-handedly dismiss all 10 academic research as being under the control of the 11 industry, if that's where the dollars come from, I 12 think that's not true. There could be a lot of 13 oversights in place that do protect the integrity 14 of the research. 15 MS. DILLEY: So maybe another way to frame 16 it, too, is, are there governance structures 17 already starting to evolve at academic institutions 18 or anywhere else that are meeting some of the 19 criteria that have been discussed, that would make 20 them more or less viable? 21 I think, Joanna, you had put up some 22 criteria. Others had mentioned other kinds of</p>	<p style="text-align: right;">Page 188</p> <p>1 their contribution to an independent evaluation of 2 a product that they, as tobacco health -- or as 3 public health servants, that they can do their work 4 and actually be viewed as having a high level of 5 integrity and independence. I think it's just a 6 reality of the playing field right now, and I think 7 it's difficult to view it any other way. 8 MS. DILLEY: Joanna, your criteria were 9 exactly for that, and I think you've emphasized 10 that the interest is meeting those criteria in some 11 way to protect the integrity of researchers at 12 institutions. 13 So I don't know if you want to speak to that 14 anymore in terms of what kind of models you see 15 emerging out there or, again, some more discussion 16 around how structures could meet those criteria. 17 DR. COHEN: Well, I think we're talking 18 about other models shortly. 19 MS. DILLEY: Yes. 20 DR. COHEN: What I see in reality -- I mean, 21 there's Jed, there's you, who's taking tobacco 22 money. There are a couple of other people, other</p>

<p style="text-align: right;">Page 189</p> <p>1 respected researchers who have. But the vast 2 majority of people that I have talked to are not 3 willing to do that because they're just not ready 4 to do that.</p> <p>5 So that's fine. Actually, if you don't 6 mind, maybe I'll ask you what you see as an 7 effective governance structure for MRTPs.</p> <p>8 MR. ROSE: First, can I just follow up both 9 on what Eric said and your follow-up? What I'm 10 hearing is that, whereas it may be possible to 11 conduct high-integrity research with sufficient 12 oversight, the fact that people believe that it's 13 not going to happen is what should dictate the 14 system, which, I mean, I could think of analogies 15 of that.</p> <p>16 But it's sort of like one could think of 17 distasteful events in the history of America where 18 there may be no reason not to associate with 19 certain people, but since everybody thinks you 20 shouldn't associate with certain people, then we 21 have to preserve the fact that we shouldn't 22 associate with certain people, whether it's due to</p>	<p style="text-align: right;">Page 191</p> <p>1 what is possible and how to make that happen.</p> <p>2 In terms of what I think is the ideal 3 oversight, I actually don't have a strong opinion. 4 I'm speaking up for the strength of academic 5 institutions just because I hear that being given 6 short thrift and unfairly so. But that doesn't 7 mean I think that's the best or the only way to 8 move it forward.</p> <p>9 But coming back to Eric's phrase "swift and 10 efficient," whether it's 448,000 people dying every 11 year or what the current figure is, we do have to 12 think of swiftness and efficiency. And if it's 13 possible to utilize existing oversight to rapidly 14 carry products forward that might save millions of 15 lives ultimately, then I think that has a certain 16 advantage over taking what might be years to set up 17 yet another oversight entity.</p> <p>18 MR. MYERS: Can I just jump in? Just a 19 quick thing. One is, we're not talking about 20 ancient history, Jed. Judge Kessler found that 21 this was going on as the case was heard, the case 22 was being tried. And she found that given the</p>
<p style="text-align: right;">Page 190</p> <p>1 color, or political beliefs, or whatever else.</p> <p>2 So I think we have to get beyond perception 3 to reality, even though many conflict of interest 4 committees do say that the appearance of conflict 5 of interest is important as well as the substance 6 of the conflict of interest. But I think that the 7 emphasis should be on substance rather than 8 superficial appearances.</p> <p>9 So in that sense, the fact that many people 10 don't feel comfortable accepting tobacco industry 11 funding is simply because of the groupthink 12 pressure that has been exerted by very vocal 13 members of the tobacco control community that tried 14 to say it's the wrong thing to do, as opposed to 15 saying that it's the wrong thing to do if it's not 16 independent, if it's not of high integrity.</p> <p>17 So if something can be done with oversight 18 that guarantees the strong likelihood of integrity, 19 at least as much as I'd say with the pharmaceutical 20 industry-sponsored trials, then I think we have to 21 go beyond the belief that it's impossible because 22 everybody has said it often doesn't happen, and see</p>	<p style="text-align: right;">Page 192</p> <p>1 tobacco industry, the companies that were before 2 her, that there was substantial reason to believe 3 that it would continue to go on. And I think 4 that's important.</p> <p>5 Second, I think all of us have said that 6 whether it's a university, the FDA, or an 7 independent entity, what's absolutely critical is 8 that there be a set of criteria. And Joanna laid 9 out ones that there are pretty broad consensus 10 behind, that absolutely guarantees the integrity of 11 what's going on, but that includes integrity of 12 agenda setting, which industry research has never 13 allowed before. They have funded research to 14 accomplish what they wanted to accomplish, not what 15 was really in the broad public health.</p> <p>16 Then the third thing you do have to deal 17 with that goes over and above that issue, which is 18 an issue with any funded research, but becomes more 19 of an issue with companies who have the history, 20 recent as well as past, that the others do, which 21 is, you want your next research grant.</p> <p>22 So it's one thing to have that concern when</p>

<p style="text-align: right;">Page 193</p> <p>1 you don't either have the history or the kind of 2 product you've got here. One has to think about 3 how you build the barrier so that the desire for 4 the next research grant doesn't -- despite all the 5 rules and regulations, despite the integrity of the 6 researcher -- implicitly bias the system. 7 So it is more complicated. But I don't 8 think there's a single one of us who have said that 9 the concept of independent research, per se, is a 10 bad idea where the researchers set the agenda, 11 where there is a break in the link between the 12 companies and the research that's being done, where 13 the researcher owns the data, where the researcher 14 doesn't have to produce results that the company 15 likes in order to be sure to get their next 16 research grant. 17 So I think you've misstated what's out 18 there, and this is not groupthink. The tobacco 19 industry is having trouble finding people to take 20 their money because of what they've done, not 21 because of what people think. 22 MR. DOBBINS: I just want to add something.</p>	<p style="text-align: right;">Page 195</p> <p>1 British American Tobacco. I would just kind of 2 like to ask the panel to expand a little bit on 3 their definition of independent. I came from the 4 SRNT conference last week, and this is the first 5 time we're starting to hear data that e-cigarettes 6 may be cannibalizing the NRT market. And then, 7 obviously, that's making NRT and e-cigarettes 8 competitive products. And then we're talking about 9 fighting for profits. 10 So would an organization or an individual 11 that takes money from PhRMA then still be truly 12 independent? 13 MS. DILLEY: Just for the people online NRTs 14 are nicotine replacement therapies. Right? I'm 15 just trying to interpret some of the acronyms. So 16 the question to the panel, a little bit more on 17 independence. 18 MR. DOBBINS: I would just actually go to 19 you, Joanna, the paper that was written really does 20 set forth a criteria of independence. And from my 21 point of view, primarily, what you want to see if 22 there are dollars that are flowing from the</p>
<p style="text-align: right;">Page 194</p> <p>1 It's not only what they've done. It's what they're 2 doing. Keep in mind 430,000 plus people are still 3 dying of the product they're selling and half the 4 people that use it die. And ultimately, many 5 people, researchers and institutions, decided that 6 is sufficient to not take the money that results 7 from that blood. 8 So I also concur with Matt, and you won't 9 hear me say anything different. The proof of the 10 pudding, the integrity of the research, will be in 11 the ability to replicate it, the ability to look at 12 the data, and I also concur the FDA developing the 13 expertise internally or through contractors 14 beholden to the FDA to evaluate the evidence it's 15 presented. 16 MS. DILLEY: So we've had a couple of 17 comments. I mean, we could do this all day. I'd 18 really like to get to a couple others. I want to 19 go to Justine and, if we have time, come back, or 20 you can ask it at the break. 21 Justine, could you introduce yourself? 22 MS. WILLIAMSON: Justine Williamson from</p>	<p style="text-align: right;">Page 196</p> <p>1 industry -- and I think Matt phrased it as a 2 complete break -- you want a complete break of 3 governance and agenda-setting. And historically, 4 in order to get that, what in actuality happens is 5 that the industry has to be forced under duress to 6 give up the money because they don't want to do 7 that, which is why the Legacy model worked. The 8 states took the money from the industry recovering 9 from the injury that was done through the tobacco 10 industry fraud. And it was the state's decision to 11 give the money to the Legacy Foundation to conduct 12 a truly independent agenda. 13 I think any -- and this is why I pointed to 14 the FDA as a model of why I would do that. The FDA 15 isn't beholden to the tobacco industry. The FDA is 16 beholden to the political controls, and any agency 17 is. And they should be making the decision about 18 what the research agenda is, not some heretofore 19 unknown third-party entity that's serving the 20 interest of getting commercial product to market. 21 MS. DILLEY: Let's take Joanna's comment and 22 then we'll have time for one more question.</p>

<p style="text-align: right;">Page 197</p> <p>1 DR. COHEN: For what it's worth, I think 2 whatever governance structure is created, it would 3 apply to traditional tobacco companies and other 4 companies for the type of research that's being 5 done. 6 MS. DILLEY: We've got one more question 7 here, and then we'll take a break. 8 MR. MOYNIHAN: Well, there have been a lot 9 of attempts to kind of broaden the discussion about 10 third-party governance and industry-sponsored 11 research, but in the case of modified-risk tobacco 12 products, the agenda is kind of set. The question 13 is the goal of how do you have a system that gives 14 people confidence in the data that is being 15 presented in support of the modified-risk tobacco 16 product applications. That's really the question 17 that I'd like to hear a more direct comment about, 18 rather than all of the other areas of tobacco 19 research. 20 MS. DILLEY: So you are asking specific to 21 modified-risk tobacco products, for third-party 22 governance? Eric? Question?</p>	<p style="text-align: right;">Page 199</p> <p>1 unique about MRTPs that shape a third-party 2 governance structure? Yes? 3 DR. PARASCANDOLA: I'm just saying -- and I 4 think it was commented before that different arenas 5 of research and data collection may require 6 different structures. I mean, obviously, they all 7 need to meet certain criteria in terms of 8 independence and integrity, but it's not clear that 9 the same arrangement will be applicable for all 10 situations. And I think -- so, yes. I would just 11 add that. 12 MS. DILLEY: Any other comments on that? 13 (No response.) 14 MS. DILLEY: All right. So we would like to 15 take a break now. We'll take the 15-minute break, 16 so we'll start back up at 2:15, and we're planning 17 to go through all the presentations on models. So 18 we have two models and then some discussion about 19 linking lessons learned to tobacco. So we'll start 20 right back up at 2:15. 21 (Whereupon, a brief recess was taken.) 22 MS. DILLEY: People, let's take our seats</p>
<p style="text-align: right;">Page 198</p> <p>1 DR. DONNY: We weren't positive what the 2 question was, so, Mike, if you could clarify. 3 MS. DILLEY: Okay. Can you repeat it? It 4 sounds like -- we've been talking about third-party 5 governance for a range of different kinds of 6 research, and you're asking specific for MRTPs. 7 MR. MOYNIHAN: Right. The question of 8 agenda setting -- the agenda -- the question -- the 9 agenda is, we have a structure, a formula, and some 10 guidance about applications for modified-risk 11 tobacco product applications. We have some 12 skepticism about why anybody would file those 13 applications and whether the data can be relied on. 14 So we have a very specific agenda in that 15 sense. And the question is, is third-party 16 governance applicable to that situation in a way 17 that's different from these broader questions? In 18 my own opinion, for example, academic research, 19 there's really nothing publishable necessarily from 20 the third modified-risk tobacco product 21 application, for example. 22 MS. DILLEY: So is there anything inherently</p>	<p style="text-align: right;">Page 200</p> <p>1 and we'll get started. 2 So just a couple of brief comments about 3 this afternoon's session. As you heard Daniel 4 Carpenter's presentation this morning, IOM sent out 5 a couple of examples just for food for thought. 6 And we have two speakers this afternoon to talk 7 about their experiences, and some models and work 8 that they're doing in terms of looking at some of 9 the issues around governance and of research. 10 Our first presenter will follow somewhat the 11 same structure in terms of we have two presenters 12 to talk about those. And then Mark Parascandola 13 will make some observations about these models and 14 their relevance to tobacco-related research. And 15 then we'll have an hour for Q&A again this 16 afternoon, after those three comments. 17 So first up, we have Richard Kuntz, who is 18 senior vice president and chief scientific research 19 and regulatory officer at Medtronic. So I'll turn 20 it over to you. 21 Presentation -- Richard Kuntz 22 DR. KUNTZ: Thanks. Good afternoon. Before</p>

<p style="text-align: right;">Page 201</p> <p>1 I talk about the experiences we've had with mainly 2 a data-sharing experience in trying to shape how to 3 make data more transparent in the process and more 4 transparent in the medical device arena, in 5 speaking with the next speaker, Eric, we thought we 6 might just give it a very quick kind of overview 7 about how devices and drugs work. 8 Our company, Medtronic, spends about 9 \$450 million a year on research, and it's 10 100 percent controlled by Medtronic. So we do our 11 own research; that is, we decide to either do it in 12 house or contract with CROs to do this stuff. And 13 the protocols for maybe between 300 and 400 14 products per year we're studying at any one time 15 are very highly regulated by the Food and Drug 16 Administration. 17 The studies are followed very carefully. 18 And if the studies are positive, we go to the next 19 level of product approval. If they're negative, we 20 don't. And so we had a handful of negative 21 products and history, where we found out the 22 product doesn't work to the standards that were</p>	<p style="text-align: right;">Page 203</p> <p>1 osteoblasts in bone, to fuse bones, mainly in spine 2 operations. So when you have degenerative joint in 3 the lumbar space and you have to have the disc 4 removed, the spine become unstable. It has to be 5 fused to the vertebrae above or below it. And it's 6 usually done by a combination of hardware that's 7 put in by the orthopedic surgeon or surgeon and 8 also fusion. 9 The standard has been to graft bone from the 10 iliac crest in the pelvis and transfer that into a 11 cage, and that's been used for 30 or 40 years. And 12 we introduced a product that actually would not 13 require you to do the harvest of the bone and 14 potentially has the same or higher efficacy in 15 actually causing fusion. 16 In 2002, there were four or five randomized 17 controlled studies that led to its approval. 18 There's a panel that reviewed it. And then there 19 are about five or six studies done subsequently 20 over the ensuing years, the last one about 2010. 21 The indications were very straightforward 22 for one level of anterolateral lumbar interbody</p>
<p style="text-align: right;">Page 202</p> <p>1 established by the FDA, and those products don't go 2 forward. And then the ones that do, we do go 3 forward. 4 About half of the studies that we do are 5 also post-market studies, looking at the expansion 6 of an existing label or uses outside the initial 7 intention with intent to go back and get a 8 re-label. Those studies are also generated by our 9 company to go forward. 10 So it's a model which inherently doesn't 11 have a sense of independence with a third party 12 overseeing that. And that would be a large 13 resource requirement, to get third parties to 14 actually look at all drug and device companies, 15 because virtually all companies work that way. 16 So I'm going to go through an experience we 17 had, where we're actually trying to push the 18 envelope on data transparency. 19 We sell a product called Infuse, which is a 20 bone morphogenetic protein, and it's made by Wyeth. 21 And it was introduced into the market around 2001. 22 And it's used to help the advancement of</p>	<p style="text-align: right;">Page 204</p> <p>1 fusion or ALIF. Based on the evidence, the FDA 2 approved the product. And peer-reviewed 3 publications, which is another layer of a way to 4 communicate, is mainly how the dissemination of the 5 information gets to physicians. 6 So think of a couple spheres of data. 7 There's data, which is all the data, all the 8 studies we do, individual patient-level data, and 9 then there's data that gets condensed and are 10 necessarily subsets, which are peer-reviewed 11 publications written by independent physicians 12 published in an independent process called peer 13 review. 14 So most of these peer-reviewed publications 15 are specifically focused on certain topics. None 16 of them ever look at the entire data set as a 17 whole, and that's generally how medical products 18 are approved. 19 In June of 2011, a major challenge was 20 raised about our product, claiming the validity of 21 virtually all of our studies, saying that in fact 22 there was more emphasis on the benefits rather than</p>

<p style="text-align: right;">Page 205</p> <p>1 the harms. And this was by a credible spine 2 surgeon, and it threw our company for a loop 3 because it really challenged all of our data and 4 suggested that the peer-reviewed publications 5 actually were not valid.</p> <p>6 The principal focus were really on the 7 results of the peer-reviewed literature. There was 8 limited or no concern about the data sent to the 9 regulatory agency early on. And we still feel that 10 the data sent to the regulatory agency was complete 11 when we re-reviewed that data.</p> <p>12 The focus was on how did the peer-reviewed 13 publications emphasize or overemphasize certain 14 benefits over harms in the peer review process. 15 And it became a challenge for us because we don't 16 participate in the peer-reviewed literature. As a 17 matter of fact, we're admonished if we do. People 18 don't want us to do ghostwriting or any kind of 19 process interacting with that.</p> <p>20 So we were challenged with trying to 21 understand how to respond to this. It was a very 22 serious accusation covered in the New York Times</p>	<p style="text-align: right;">Page 207</p> <p>1 policy issues about how to make data transparent, 2 and they had a huge interest in trying to do this.</p> <p>3 We agreed to take all of our data, patient- 4 level data, to de-identify the data, have it 5 audited -- that was for 14 studies -- and take all 6 of the adverse event reports that we sent the FDA 7 over the last 12 years, and all of the e-mails 8 between the FDA and so on, and give that to Yale.</p> <p>9 Then Yale, in their group, decided to -- we 10 then stood back. We did not set the agenda. We 11 said, "Here's all the data. Figure out what the 12 issues are. Read these papers about what the 13 concerns are. But what we'd like you to do is to 14 provide for us a systematic review of our data so 15 that we can understand what the truth is."</p> <p>16 So they took that data. We stepped back. 17 We funded it. It was about 2 and a half million 18 dollars to fund. And we were very careful about 19 making sure that we looked at where that money was 20 being spent, and it was reasonable that it was 21 being spent for things exactly as expected, the 22 data processing.</p>
<p style="text-align: right;">Page 206</p> <p>1 and seven or eight other publications. I was on 2 the phone with Barry Meier the day after this broke 3 out, and we had to really review a bunch of papers 4 that came out, re-review our history, and take a 5 stand.</p> <p>6 So we decided that we were not going to 7 fight a battle of our interpretation versus someone 8 else's interpretation because it would be 9 inappropriate. We also felt it was responsible for 10 us to make sure that the public could trust us and 11 view what this means. And we also wanted to 12 understand whether or not these claims that were 13 made were actually true, because if they were, we 14 needed to take action on the product.</p> <p>15 So we decided to take a process to try to 16 establish what would be viewed from the public as 17 an independent process to review the data. And 18 what we did was, we worked with some colleagues 19 that we had loose connections with at Yale, who had 20 mainly an interest in data transparency. And we 21 felt that that would be a good group to work with 22 because they had already worked through a lot of</p>	<p style="text-align: right;">Page 208</p> <p>1 They contracted two separate, independent 2 groups to do a systematic review. And they chose 3 two academically established groups. One was the 4 Oregon Health Sciences University, OHSU, and the 5 other was York in England, both of which are 6 distinguished systematic review groups.</p> <p>7 So the connection between the systematic 8 review groups who were going to evaluate our data 9 was with Yale, not with our company Medtronic. Our 10 relationship to Yale was to de-identify and give 11 all the data to fund this activity, and then let 12 Yale set the agenda about this. So Yale chose the 13 systematic review sites, and they established the 14 steering committee to review this.</p> <p>15 The principals for this project -- and there 16 was a chance that Harlan was going to be here to 17 talk, but he had a conflict. And I'm not going to 18 get into too much detail because it's really not 19 appropriate to explain all of their processes, but 20 I'll give you some high-level overview.</p> <p>21 Harlan Krumholz is, I think, a distinguished 22 health quality and health services researcher. He</p>

<p style="text-align: right;">Page 209</p> <p>1 is the editor of Circulation Quality, and he has a 2 group who has a major interest in understanding how 3 to make data more transparent. So we worked with 4 him.</p> <p>5 He also assigned a steering committee to 6 oversee this independent from him, just to make 7 sure that there would be no concerns about his role 8 in contracting with Medtronic, and that was headed 9 by Zeke Emanuel, who had been on Obama's staff 10 early on and helped shape the Affordable Care Act. 11 And he led a group of distinguished individuals, 12 about 15, one of which included Deb Zarin, for 13 example, who runs the clinicaltrials.gov and 14 others.</p> <p>15 So we tried to develop what we thought would 16 be a beyond-reproach group of individuals who have 17 a history of not being influenced and also would be 18 able to look at this case. So that's the basic 19 structure.</p> <p>20 The deliverables were that the systematic 21 reviewers would produce two formal systematic 22 reviews, and then the publication of that would be</p>	<p style="text-align: right;">Page 211</p> <p>1 summaries of these systematic reviews. That will 2 be followed by the full systematic reviews, which 3 are essentially these phone book-type detailed 4 analyses of all of these studies.</p> <p>5 Then on the third part, we decided in 6 concert with Yale that we would make all that data 7 publicly available. So the patient-level data that 8 we gave to the systematic reviewers would then be 9 made available to the public. And we're in the 10 final process here, understanding how to make that 11 dissemination, which is going to be a process we 12 follow about how we take requests, and give the 13 data out, and so on. And this is where we're 14 finalizing that process. And we're anxious to 15 understand what that means.</p> <p>16 So that's the overall structure, per se. I 17 wanted to show just a little bit about some of the 18 processes involved in getting this data. It was 19 very complicated.</p> <p>20 In order to get the initial data that we had 21 in our data warehouse for these studies that went 22 back 10 or 12 years and make them available for</p>
<p style="text-align: right;">Page 210</p> <p>1 through a contract with the Annals of Internal 2 Medicine, which is a top-tier journal in medicine. 3 That would be, as a manuscript, summarizing 4 systematic reviews. The sequence was that the 5 systematic reviews would be produced. The 6 systematic reviewers gave their initial reports to 7 Yale and to us. We were able to make comments 8 about that. They were not in any way obliged to 9 follow any of our comments, and Yale made comments 10 back to them. They essentially had the opportunity 11 to revise as systematically as they wanted to or 12 not. And we have not seen any results of that 13 second round yet, and they are completely 14 independent to do that. And they are in the 15 process of finally getting the papers published.</p> <p>16 This has taken us a little longer than we 17 thought it was going to take because we thought it 18 would be done within a year. It's been almost two 19 years, but that's just the process of publication 20 and reiteration. It was completely independent on 21 our part. So we expect in June to see the 22 manuscripts being published for these. There are</p>	<p style="text-align: right;">Page 212</p> <p>1 systematic review, we had to go through a HIPAA 2 de-identification process, and that was a very 3 timely and costly process. Hopefully, if we get 4 experience, we'll learn how to streamline this 5 further. And these are not meant to be read, but 6 we had extremely difficult --</p> <p>7 MS. DILLEY: That's good</p> <p>8 DR. KUNTZ: -- processes to follow. And 9 overall, we -- there's an individual I have in 10 here, and I'll speed through them because I don't 11 want to waste time -- did hire a -- well, actually, 12 Yale hired -- we paid for it, but Yale hired an 13 expert. And there are these experts. This is a 14 person on faculty at Columbia, who our experts and 15 certified to do de-identification. And you have to 16 de-identify about 13 different fields of the data 17 in order for it to be processed.</p> <p>18 So this is a first-ever in industry, in the 19 drugs or devices, to ever do what we have done. So 20 we were a little bit blinded in trying to 21 understand how to go forward. So my guess is that 22 we were very inefficient in some of our processes,</p>

<p style="text-align: right;">Page 213</p> <p>1 and that's why it cost \$2.5 million to do this one 2 project. We don't think that to do this again is 3 going to cost that much money as we start to get 4 more efficiency. But what we were really focusing 5 on was really understanding how to make sure that 6 we could be trusted to say, "You know what? If 7 there were mistakes made in our product, we need to 8 know it as well as anybody else does, and we need 9 to take appropriate action." But the first part is 10 to really get the truth, and try and understand 11 what that means.</p> <p>12 Understanding that, with the discussion 13 earlier today, that one would like to have total 14 independence, one has to also understand whether 15 there are resources available for those independent 16 groups to do that. And since the profit-making 17 companies like ours have dollars that we can spend 18 on that, how do we basically take those dollars and 19 directly put it into a system that can still be 20 beyond reproach and be independent.</p> <p>21 So we're anxious to see the final results of 22 how this comes out. We're anxious to see whether</p>	<p style="text-align: right;">Page 215</p> <p>1 but to liberate a lot of data to individuals who 2 don't have methodological training, especially some 3 of the complicated analyses, may cause individuals 4 to find the wrong results. And there is still an 5 appetite, on the media side and others, even 6 journals, to publish sensational and outlier-type 7 results. So we want to understand how to move to a 8 space that becomes a little bit safer, so that we 9 can get actually the truth as we start to 10 disseminate this product.</p> <p>11 We're committed to making the data publicly 12 transparent, but we know there will be some 13 turbulence in a way. Our announcement that we're 14 going to make the data publicly available has 15 already led to internet sites from plaintiff 16 attorneys in Manhattan, who have already requested 17 people to say, "When we get this data, please let 18 us know if you've been harmed by our product 19 because we're going to try to analyze the data." 20 So we knew that, that was going to happen anyway. 21 And so we're trying to figure out what the process 22 is.</p>
<p style="text-align: right;">Page 214</p> <p>1 our industry colleagues, our competitors, and other 2 people in the drug and device industry think this 3 is a good experience or bad experience. We want to 4 make sure that it looks like a good experience 5 because we're true believers that data transparency 6 is very, very important to go forward.</p> <p>7 We certainly would like to, as an industry, 8 compete on the technologies that we make and not on 9 whether we hold data back, and I think that's also 10 going to level the playing field to make it a lot 11 better. And I think everybody's in agreement that 12 that's probably the right way to go.</p> <p>13 I want to end just with a few comments about 14 what concerns we have when we look at the 15 transparency part. To make data transparent is a 16 little scary. We have complex data that when held 17 in silos and shielded from everybody are 18 concentrated. People actually know how to do 19 analysis and are actually very concentrated. And 20 then this is shared by Food and Drug Administration 21 people who also do these kind of analyses.</p> <p>22 That's probably not the best configuration,</p>	<p style="text-align: right;">Page 216</p> <p>1 So we want to know, for example, when we get 2 a query, who is asking the question and why. Not 3 that we would ever bar a plaintiff attorney's law 4 office or group to be able to ask a question; they 5 have just as much right as anybody to ask 6 questions. We kind of want to understand what the 7 question is to make sure that they're not trying to 8 look at something that's just purely a money-driven 9 approach on their part.</p> <p>10 Should we limit these queries to one 11 question at a time? This is what they do in the 12 U.K. The U.K. has a transparent policy. They 13 limit it to one question at a time, and they 14 license the question. I'm not trying to ask the 15 questions rhetorically to say we're going to come 16 up with the answers, but these are things that you 17 would have to go through if you're going to make a 18 transparent process.</p> <p>19 What about access? Do we just put this in 20 an Excel spreadsheet and just send it out? That 21 probably is inappropriate this time. Do we 22 actually have another third party maybe help</p>

<p style="text-align: right;">Page 217</p> <p>1 individuals who don't have the talent to be able to 2 review or analyze stuff, do that independence if 3 they know what the question is? These are 4 questions we have to look at. 5 Then, finally, the methods are really 6 critical because we spend a lot of time on product 7 reviews, months with the FDA and panel to determine 8 how to actually answer the questions we're asking, 9 how to make sure we preserve type 1 error, how to 10 make sure that we don't go overboard and analyze 11 stuff up front here. 12 When we give and liberate a lot of data, 13 there's a massive opportunity for type 1 error, for 14 people to find a lot of probabilities. So how do 15 you disseminate the information to make sure that 16 the findings are treated as hypothesis-generating 17 rather than as results of studies going forward, so 18 that people don't get harmed, or that we don't 19 exaggerate claims that we actually don't have. 20 The data-sharing part is really looking at 21 how do we slowly disseminate this out further to 22 people with or without those talents. And I'll</p>	<p style="text-align: right;">Page 219</p> <p>1 review, that's probably not appropriate. However, 2 there are plenty of examples where principal 3 investigators are just as motivated to make things 4 look as good or better than the industry may do, or 5 that they may actually be well intended, but may 6 not analyze the data correctly because they don't 7 have the skillsets and that happens a lot. 8 So we need to understand -- and we do this, 9 by the way. We have several businesses, and I can 10 tell you many examples, where our side actually 11 cautions the principal investigators to not make 12 these claims because they're not real, and we talk 13 to this all the time. Nobody ever covers that in 14 the New York Times, by the way, but that happens a 15 lot in our company. But there are no rules about 16 this up front. 17 So anyway, that's the model that we did. 18 It's a 15-minute conception of a very complicated 19 process that we went through. I outlined, I think, 20 a little bit of the structure about what we try to 21 do to answer these questions to go forward with the 22 main intent to have high integrity on our part.</p>
<p style="text-align: right;">Page 218</p> <p>1 just go to my last slide here. 2 I think what one of the most important 3 questions that we want to disclose in this space is 4 what our role is on the industry side. And I'm 5 from academics, so I've got sensibility about what 6 the academic side is as well. But in industry, it 7 was our role? 8 Our role principally is to work with a 9 regulatory agency, and make sure that we follow 10 regulatory guidance, and make sure that we get a 11 product that has regulatory results that meets 12 standards so that patients can be informed. 13 We currently work with a separate sphere, 14 which is the peer-reviewed literature sphere, where 15 principal investigators publish and take our data 16 and publish it in that realm. And that is 17 regulated by two reviewers, and a publication, and 18 a journal. And in many cases, it's very difficult 19 to understand whether or not we have a role in 20 policing the peer-review process. 21 It sounds a little ironic. The 22 industry-policing, peer-reviewed, independent</p>	<p style="text-align: right;">Page 220</p> <p>1 We feel, and our CEO feels, that we can 2 weather the storm of a product that may have had 3 some problems that we may have had to take off the 4 market. We can deal with that. What we can't deal 5 with is having anybody view us as not having high 6 integrity because that's where companies go down. 7 So we need to maintain that philosophy that 8 we can be trusted at every level, even at the risk 9 of saying that we made a mistake or that there is 10 data that came up and we need to pull something off 11 the market. That's a structure that we want to 12 develop. But there are derivatives of that, and 13 that includes issues about how do you go to this 14 next level of responsible data sharing and handle 15 the processes. And I'll stop there. 16 (Applause.) 17 MS. DILLEY: Thank you very much. So I'm 18 going to start with an e-mail question, if I could, 19 because I'm very excited that we got one that was 20 e-mailed. 21 (Laughter.) 22 MS. DILLEY: So the question for you,</p>

<p style="text-align: right;">Page 221</p> <p>1 Richard, is what will you do if the results are not 2 favorable? I think you've already referenced that. 3 And then a second question, do you plan to use a 4 similar process for other products? 5 DR. KUNTZ: Good questions. We'll act 6 appropriately whatever the findings show. And the 7 actions will be everything from taking the product 8 off the market to reinforcing the claims, if 9 they're shown to be important, to modifying the 10 claims, to inform patients that there are high 11 risks that we had talked about before, that they 12 need to be informed on. So it's a continuum. 13 There is some room for products to be able 14 to inform people about benefits, and risks, and the 15 changes in that ratio. And then there's a point 16 where the ratio becomes unfavorable, and you need 17 to take a product off the market. As the product 18 becomes less beneficial and more risky, then we 19 have to focus on those individuals who most benefit 20 from the case. 21 So in the case of BMP, we know that there 22 are some patients that have osteoporosis that just</p>	<p style="text-align: right;">Page 223</p> <p>1 product. What we want to do is make sure 2 that -- I'm very concerned about jumping out too 3 far ahead at this point because if we get burned, 4 it'll really push industry back many years. 5 This is something I think that the Yale 6 group is very cognizant of. Of course, they would 7 like to get instant transparency immediately, but 8 they also know the practicality that if in fact we 9 put three or four products on the market right now 10 and then we had ended up with hundreds of millions 11 of dollars of lawsuits, we know that our industry 12 colleagues will pull back the circle wagons and 13 say, "This is not what we're going to do." 14 So we want to have this as a good experience 15 going forward, but we do intend to bring, within 16 the next year, another two products to the public, 17 and then try to get broader as we start to 18 understand how this stuff works. 19 MS. DILLEY: Great. 20 Joanna, you had a question?. 21 DR. COHEN: Joanna Cohen from Johns Hopkins. 22 Just a question of clarification. It's your slide</p>
<p style="text-align: right;">Page 222</p> <p>1 don't have good responses from normal therapy, and 2 this is what they need. And they may actually 3 tolerate a higher risk-benefit ratio if that comes 4 up. But the individuals who would have perfectly 5 good responses from alternatives, that may cross 6 their threshold and they decide not to use this 7 product because the risk profile has changed 8 overall. 9 So I think what we would want to do is just 10 make sure that we look at this, and we intend to 11 use third parties to also gauge this risk as well, 12 so that we can make the appropriate part. But the 13 relationship we've had with the FDA has been very 14 good, and I think, in general, they'll weigh in 15 very heavily on how they look at this data and 16 whether or not they think action should be taken as 17 well, and we'll follow that appropriately. 18 MS. DILLEY: So they obviously get that 19 information at the same time. Right? 20 DR. KUNTZ: Yes. And the second part of the 21 question is, will we do this for the data? Yes. 22 We will. We're actually looking at the next</p>	<p style="text-align: right;">Page 224</p> <p>1 number 8, which is communication, logistics, and 2 boundaries. And you had some bullets of the team 3 can communicate about certain things and the team 4 cannot communicate. So my first question, is that 5 your team? 6 (Brief pause.) 7 DR. COHEN: So the team is who? And my 8 second question is what's the difference between 9 study conduct and evaluation methods? 10 DR. KUNTZ: I'm not quite sure exactly what 11 they meant on here because its the internal part. 12 I can tell you that we designed this to make sure 13 that -- we wanted to make sure that our team didn't 14 influence in any way the processes that we did. 15 So when we talk about evaluation 16 methodologies, we wanted to make sure that they 17 were free to do evaluations differently. We had 18 some insider baseball approaches that we used in 19 evaluation of products. And so when we discussed 20 how we would do the data, the first part was, we 21 can give you studies we've done and so on, but we 22 want to be very careful about understanding the</p>

<p style="text-align: right;">Page 225</p> <p>1 algorithms, assess codes that we use to evaluate 2 the methods to make them freely available. 3 There is nothing nefarious here. We in many 4 ways want to make sure that everybody got all the 5 data we had, but we were restricting some of the 6 things. We might be viewed as being influential if 7 we were to tell them, this is how we did the 8 principal analysis of the study. This is why we 9 think we showed benefit. Here's our methodology 10 used. In situations like that, we said we weren't 11 going to do those evaluations. And that may be 12 what that states here. 13 MS. DILLEY: So that's trying to set up the 14 firewall between what information you're doing and 15 what you think might influence the -- 16 DR. KUNTZ: Yes. These processes were 17 actually a team effort between Yale and us to say, 18 okay; how are we going to keep this data together, 19 with an idea towards making sure that we show this 20 publicly; it would be clearer. But I know we 21 failed on that. So I'll try and make that more 22 clarifying.</p>	<p style="text-align: right;">Page 227</p> <p>1 re-analysis before you ever got approval for a 2 product? 3 DR. KUNTZ: Yes. So this is a really 4 interesting question. The way that devices -- and 5 I think drugs -- is that we do pre-market studies 6 to meet some endpoint, usually in time, to get 7 approved. And usually, those endpoints are on the 8 one- to two-year range. However, there's a huge 9 interest in long-term durability, risks of things 10 like cancer and other stuff like that, that we 11 can't necessarily wait for. Otherwise, you're 12 going to get technology that's very, very stale. 13 So we hope that that handoff will happen in 14 the post-market. And it's one of the reasons we do 15 post-market studies. We continue to follow those 16 patients and new cohorts for a longer period of 17 time and update that. So that's one of the reasons 18 that we do post-market studies. And then, we're 19 also introducing the concept of doing more 20 appropriate surveillance to look at those as well. 21 So we don't necessarily do a systematic 22 review in the pre-market application for the PMA</p>
<p style="text-align: right;">Page 226</p> <p>1 MS. DILLEY: Redesign on the boxes. 2 Do you have a question over here? 3 MR. DILLARD: Richard, Jim Dillard. Altria 4 Client Services. A clarifying question, and then 5 maybe a little bit bigger question, which is, if I 6 have this right, there was about 14 studies. They 7 were all pre-market studies that were done. 8 DR. KUNTZ: No. About half. 9 MR. DILLARD: About half. And then that 10 other half is what you've been doing in the 11 post-market period. 12 DR. KUNTZ: That's correct. 13 MR. DILLARD: So you took all that data and 14 did what this appears to be as a post-market 15 re-analysis of sort of the ongoing data up to that 16 point. Is that correct? 17 DR. KUNTZ: Correct. 18 MR. DILLARD: I've got that clear. 19 Would you ever venture down this particular 20 pathway and do something similar -- I probably 21 can't answer it at this point, but you've thought 22 about it, I'm sure -- as a secondary data</p>	<p style="text-align: right;">Page 228</p> <p>1 together. We just get the data in, and then 2 they're actually listed as separate trials. But I 3 think we are starting to see some value of doing 4 large, systematic reviews of all of our data to be 5 able to track rare events and other things as well. 6 And we're doing that for coronary studies, for 7 example, and others, especially when you start to 8 collect data sets where there isn't enough power to 9 look at these rare events in individual groups 10 themselves. 11 So, yes. We are going to be doing more 12 systematic reviews of our products overall, not 13 only because we're curious, but because the demands 14 of the people who make the buying decisions want to 15 know that data as well, including the patients and 16 caregivers. 17 MS. DILLEY: We have time for one more 18 question. Does anybody have a question? 19 (No response.) 20 MS. DILLEY: Great. Well, we'll come back 21 to you after Eric gets his presentation, and Mark 22 as well.</p>

<p style="text-align: right;">Page 229</p> <p>1 So next up, we have Eric Peterson, who is 2 the Fred Cobb professor of cardiology in the 3 Department of Medicine, director of the Duke 4 Clinical Research Institute, and the director of 5 performance improvement for the Duke Heart Center. 6 You even have time to give other 7 presentations elsewhere. Thanks for being here. 8 Presentation – Eric Peterson 9 DR. PETERSON: Thank you very much. Just 10 another comment on that last question. In part, 11 there is another entity that has access to all 12 those studies and can do those meta-analyses. 13 That's called the FDA, when it's going into the 14 pre-market setting. So theoretically, it is a 15 third party that's overseeing, at this case, the 16 regulatory party. 17 Before I begin, I'll do some disclosures. 18 In part, I am part of an academic university. I do 19 here -- although we don't know anything about any 20 tobacco monies that ever come in to our institute, 21 at least as a part of this -- however, we do 22 receive a fair degree of our funding -- up to a</p>	<p style="text-align: right;">Page 231</p> <p>1 worlds that have lived in very different and 2 sometimes highly competitive worlds, maybe three. 3 In part, there is academic centers. And you heard 4 this morning about experts in the field. We're 5 trying to marry that with the abilities of a 6 contract research organization, or CRO, 7 conceptually that we can do the parts of research 8 to produce high-quality, very efficiently run 9 research, but now married to this mission as 10 opposed to married to a bottom line that's going to 11 produce a profit. 12 So rather than being a standalone industry 13 that's going to produce me as the executive, a fair 14 degree of money, unfortunately for myself at least, 15 this is more about the mission of trying to produce 16 better evidence. 17 The DCRI grew. It's sort of an interesting 18 history. I won't give you the full story of it. 19 But it was started by our first chairman of 20 medicine, who took a government grant that was 21 supposed to be about how we might use computers to 22 better understand systematically how patient care</p>
<p style="text-align: right;">Page 230</p> <p>1 little over half to two-thirds of our money does 2 come from the device or drug industry with regards 3 to both on the pre- and post-market effort to try 4 to establish the evidence and is ultimately to 5 drive those into practice. 6 We are by our title, and at least our own 7 claim, the world's largest academic research 8 organization in terms of the types and quantities 9 of work we do. We're over 1300 people right now, 10 working on our single institution, devoted to this 11 single mission. And we believe very strongly in 12 this, this idea that we are, in part, charged to 13 help develop and share knowledge around the world 14 to improve patient care through innovative clinical 15 research. 16 Conceptually, this is the idea that we, in 17 part, want to try to get the best evidence known, 18 and then to share that in a manner that helps 19 patients, and then to try to do it around the 20 world, and ultimately to drive it into clinical 21 practice. 22 In concept form, it's the mergers of two</p>	<p style="text-align: right;">Page 232</p> <p>1 should be delivered. He took that data, collected 2 information on however patient with cardiac at Duke 3 was treated with an idea that if we learned what 4 was being done, maybe we could learn better how to 5 do the next one. 6 That created a generation of statisticians 7 and clinicians working together, and ultimately 8 created the need for maybe observational data alone 9 wasn't enough to answer these questions, so we 10 would do randomized clinical trials, which then led 11 to the world's largest, at that time, clinical 12 trial, the GUSTO study, which then launched a whole 13 series of other studies after that, and that became 14 us. It has now expanded into a lot of different 15 realms, and I'll go through just a few of those. 16 If you take it at its whole now, we do sort 17 of three forms of research. There is clinical 18 trials, everything from the earliest phase 1 or 19 first-in-man studies, all the way through phase 4 20 type of research, post-market studies. 21 A lot of that research is done with the 22 government. We conduct large studies that</p>

<p style="text-align: right;">Page 233</p> <p>1 are -- large network trials with NIH in particular, 2 but with other agencies as well. And then with 3 industry, as we mentioned before, in part, these 4 are often looking at a specific product, does it 5 work or not, and helping to develop with industry 6 in those cases whether or not those drugs or 7 devices are safe and effective when used in humans. 8 We also do outcomes research, which is the 9 idea that we might use evidence that's available in 10 other forms, either from claims or clinical 11 registries to, in part, learn about the safety and 12 effectiveness of drugs or devices when used in 13 routine clinical practice, and where there are gaps 14 in care, and ultimately to drive that forward. 15 Finally, we're getting more and more into 16 the educational sphere, and I'll talk about this 17 later. But, conceptually, this is another one for 18 which huge conflict of interest issues have 19 certainly limited the scope and quality of research 20 or quality of education that exists out there, and 21 it's our goal to sort of expand that role as well. 22 We believe that, like a CRO in part, we can</p>	<p style="text-align: right;">Page 235</p> <p>1 lot of discussion about that before. In part, 2 there is a combination of forces that come together 3 to create a study design. Many of it are set forth 4 by the FDA under their regulations. Scientific 5 experts come together, coordinating group come 6 together with co-chairs, often international 7 representatives from science in the field, to 8 create the study design. 9 Then that's taken to the FDA and, again, 10 there is a blessing and a hand-off between those 11 two groups to say, this is an acceptable or 12 unacceptable design; your control was accepted, 13 et cetera. All those kind of questions are vetted 14 backwards and forward until an actual final study 15 design is created. 16 Sponsors do work with that, in part, 17 absolutely. But, again, it is a collaborative 18 process to try to get the best science with 19 regulators on the top of it to make sure that the 20 process is ultimately fair. Data safety monitoring 21 boards are out there to monitor the activities and 22 safety for the patients that are involved, and</p>
<p style="text-align: right;">Page 234</p> <p>1 provide all the expertise on how to execute a 2 study, the operational component pieces, but also 3 have, from a design perspective, the ideas that a 4 clinician and a regulator might want in terms of 5 how to develop the best evidence; and then 6 ultimately the analysis capability to carry out 7 that research, get to the right question; and then 8 hopefully the role of education to try to teach our 9 peers and the public what we ought to be doing with 10 this evidence. 11 We do this on a global basis. We have 12 partnerships now. There's a BCRI in Brazil. We 13 have many partnerships in China. We have a few 14 partnerships in India and partnerships in 15 Singapore. In part, research has gone global and, 16 in part, we now want to partner with either 17 academic research organizations around the world 18 or, alternatively, our own partnerships to try to 19 further these research activities. 20 Just a few words I put in this slide -- this 21 isn't in your packet, I'm sorry -- to try to get an 22 idea of how these studies are created. There was a</p>	<p style="text-align: right;">Page 236</p> <p>1 clinical events' committees adjudicate the degree 2 to which the accuracy of many of the elements, in 3 particular the endpoints, that come out of the 4 study itself. 5 As we mentioned, that's sort of on the trial 6 side. On the observational research side, there's 7 a whole plethora of data that I won't be providing 8 today, that talks about how we might look at real- 9 world information to try to create a more clinical 10 knowledge. 11 We're getting more and more sophisticated at 12 using data from either electronic healthcare 13 records or, alternatively, clinical claims models 14 of data, linking data in various fashions, linking 15 it now to genomic and other information, 16 biomarkers, et cetera, even now looking at the 17 drugs or devices, to create better evidence from 18 comparative effectiveness and comparative safety 19 studies. 20 Then finally, we're moving to a world where 21 there's not going to be this division between 22 observational data from registries and clinical</p>

<p style="text-align: right;">Page 237</p> <p>1 trials, but there will be hybrids created. And 2 we're working very fast at trying to create 3 practical clinical trials. In our view, this 4 concept of registries and trials working together 5 much more fluidly will ultimately produce cheaper 6 but more accurate studies, maintaining the role of 7 randomization, but in fact trying to make these 8 things a part of routine clinical practice when 9 there is a lack of evidence about what the best 10 thing is to do.</p> <p>11 This probably will be less appropriate for 12 devices or drugs that are new to market, but more 13 appropriate for things that we might be using or 14 standards we might be using out there, but we don't 15 know which one is the most appropriate.</p> <p>16 We are carrying out these right now -- this 17 isn't all just sort of myth and future hype -- in 18 part, with the Cardiology Society of America, who 19 holds their national registry. We are the analytic 20 center. We're creating a randomized clinical trial 21 of two techniques on how to access your coronary 22 arteries in women to do angioplasty procedures</p>	<p style="text-align: right;">Page 239</p> <p>1 then there is some work even beyond that, efforts 2 to use electronic healthcare records across major 3 healthcare systems, called the Collaboratory 4 Effort, sponsored by the NIH. We are the 5 coordinating center for that activity, to try to, 6 again, stimulate more clinical research in very 7 practical clinical studies'; again, emphasizing the 8 role of randomization, but trying to do it in a 9 much more simplified fashion.</p> <p>10 We produce a lot of papers out of this 11 activity in any one year out of the DCRI. It's 12 nearing almost 900 publications that come out of 13 that. Over 20 percent or more will be in what we 14 call top-tier or high impact journals, so the peer 15 review process is a large part of what we have to 16 go through.</p> <p>17 But I will emphasize just one point upon 18 that factor that came up earlier about how to avoid 19 spurious findings. Rick mentioned this earlier. 20 But we believed very fully that part of this can be 21 gotten around by actually having, just like within 22 a clinical trial, investigators put up front what</p>
<p style="text-align: right;">Page 238</p> <p>1 through the groin or through a wrist procedure. 2 This will be a randomization at the level, but the 3 data is all collected within the registry itself, 4 so making a much more efficient study.</p> <p>5 Then probably the most unique hybrid that is 6 coming out now through the collaborations of the 7 professional societies is a new device for 8 percutaneous opening of heart valves, percutaneous 9 placed aortic valve.</p> <p>10 This has industry partners, the FDA, CMS, 11 and the professional societies, as well as an 12 academic party, all working together to impart 13 every patient that's going into these, who have 14 these new devices put in. They'll be put into a 15 national registry. That will be used for both 16 research purposes, ultimately post-market 17 surveillance; and then even extensions of 18 indications in settings where they think they don't 19 need a randomized comparison.</p> <p>20 Ideally, this will have multiple industry 21 partners playing, using all the same registry, so 22 it can happen when done in a right setting. And</p>	<p style="text-align: right;">Page 240</p> <p>1 the actual question they're going to ask is, what 2 the endpoints are, how they're going to analyze the 3 data to avoid fishing expeditions.</p> <p>4 I am also one of the editors for JAMA, and I 5 am trying to press this very hard into action, so 6 that we will be able to have a pre-specified 7 analysis plan, to be looked at, at the same time we 8 have a journal article, particularly those when 9 used in observational research.</p> <p>10 Then finally, we are doing a fair degree of 11 work of trying to push this data out into the real 12 world -- I won't go through that today -- as well 13 as efforts to try to improve the continuing medical 14 education process, which has also challenged some 15 of the discussion earlier about how will these 16 messages be conveyed to the public, apropos here.</p> <p>17 We're trying to develop the academic centers 18 to be a home where high-quality education could be 19 developed, but hopefully in more innovative 20 strategies than have been used in the past. So 21 that was a quick run-through. 22 (Applause.)</p>

<p style="text-align: right;">Page 241</p> <p>1 MS. DILLEY: Why don't we just take some 2 quick questions for Eric? And then Mark is going 3 to come up and talk a little bit, then we'll go to 4 our panel. But for Eric, questions for 5 clarification? 6 MR. MYERS: Who designs the studies? Do you 7 do it or does the company, or is it a partnership? 8 DR. PETERSON: Yes. I will repeat the 9 question. Who designs the studies? And in that 10 regard, it's a partnership between the academic 11 center and the sponsor, ultimately the FDA having a 12 large oversight in terms of okaying or not okaying 13 the design that's been put forth if it's an 14 investigational drug or device. 15 MS. DILLEY: Other questions for Eric in the 16 overview? 17 DR. PETERSON: One more question, I guess. 18 There was discussion earlier today about the degree 19 of independence and how that would be maintained. 20 And I think most academic centers, we had to sign a 21 pretty strict contract with our legal services that 22 would say that any data that we've gone down the</p>	<p style="text-align: right;">Page 243</p> <p>1 MS. DILLEY: So Mark, I know you were going 2 to start thinking around translating some of this 3 information that both Richard and Eric have 4 provided to some of the questions raised this 5 morning on third-party governance for tobacco- 6 related research. So we'll turn it to you and then 7 we'll have you set up with the other two. 8 Discussion (continued) – Mark Parascandola 9 DR. PARASCANDOLA: So great. I think it is 10 helpful to hear examples of how, at least in other 11 research arenas, people have implemented research 12 governance structures. And I think this is helpful 13 to get us started. 14 These are certainly rigorous models, I 15 think, for research governance. But I just want to 16 move us into a discussion just to give a few brief 17 bullet points about special issues that may be 18 addressed in trying to do a similar thing in 19 tobacco product research. 20 So first of all, I think the issue of ethics 21 in human subjects protection, that's kind of built 22 into clinical research endeavor in these days</p>
<p style="text-align: right;">Page 242</p> <p>1 road of saying we're going to investigate these 2 things, we have a right to the data, to publish it, 3 to use it for any publication that we want to go 4 forward with. Industry has a right to see what we 5 will be putting out and comment on it, as mentioned 6 by Rick, but not to rewrite what we are or to 7 withhold that data from publications. 8 Just to tell you, in my experience, while 9 there are bad experiences out there, I've had more 10 difficulty publishing things from my own 11 professional society than I do from industry. But 12 you could argue whether one's in industry and one's 13 not. 14 MS. DILLEY: Another question? 15 MS. COHEN: This question is for Duke. What 16 role does a funder play in design, conduct, and 17 decisions about publication of research? Are any 18 of the concerns raised this morning about 19 independence of researchers addressed? 20 DR. KUNTZ: Yes. I think there might have 21 been a time lag, and I anticipated the question, so 22 I think I handled most of those issues.</p>	<p style="text-align: right;">Page 244</p> <p>1 because of regulations from both FDA and also that 2 apply to NIH-funded research. But before the 3 Center for Tobacco Products, tobacco product 4 research that was not funded by NIH was in kind of 5 a no-man's land because it didn't fit under -- if 6 it wasn't funded by NIH, they didn't have to follow 7 the common rule as a PHS-funded research does. And 8 if it wasn't submitted to the FDA as part of a new 9 drug application, they didn't have to fulfill those 10 requirements. 11 So I think, first of all, it would be 12 helpful to have some more attention to application 13 of the common rule to human subjects research 14 that's conducted in the context of an application 15 to CTP. And I think also it's important to 16 consider the human subjects protection in this 17 research context. So at NCI, we have seen a number 18 of unique ethical challenges or questions posed by 19 IRBs to our grantees. IRBs have different views 20 about how to assess the risk-benefit ratio in 21 evaluating potential modified-risk tobacco 22 products.</p>

<p style="text-align: right;">Page 245</p> <p>1 Some IRBs have raised concerns about giving 2 an experimental tobacco product to research 3 subjects. The product itself, of course, poses 4 risks and then there may be other risks that are 5 unknown. And so we really kind of lack guidelines 6 here for how to evaluate those kind of risk-benefit 7 questions in the context of potential modified-risk 8 tobacco products. So I think that's an area we 9 need to look more attention to.</p> <p>10 The second point I wanted to make is I think 11 we need to have more attention to what the scope of 12 industry-funded research is that we're talking 13 about under these governance models. I think this 14 is the theme that actually came up already this 15 morning, so I'm not going to say a lot about it.</p> <p>16 Not all research projects may require the 17 same governance model. We might distinguish, for 18 example, as has been said this morning, between 19 studies that are conducted in the context of 20 providing data for a specific modified-risk tobacco 21 product application versus studies that are 22 conducted to develop novel methods for assessing</p>	<p style="text-align: right;">Page 247</p> <p>1 context of the pharmaceutical industry may not 2 necessarily be the same in the case of tobacco. 3 Fourth, transparency and access, of course, 4 is key. And I think Dr. Kuntz mentioned that, 5 sometimes, opening up a data set can be scary. And 6 I think this is a double-edged sword, that of 7 course we want to promote transparency, but also 8 data can be re-analyzed and manipulated in ways 9 that are counter to the investigator's intentions 10 and counter to public health. So that's, I think, 11 additionally a concern we want to address.</p> <p>12 And finally, there is certainly a burden 13 imposed on industry to meet these standards. And I 14 think that's appropriate because the stakes for 15 public health are very high in assessing or 16 evaluating a novel potential modified-risk tobacco 17 product.</p> <p>18 So there's a burden on industry also to 19 show, through their behavior, that they are 20 conducting and supporting rigorous and valid 21 science. Again, Dr. Kuntz mentioned that Medtronic 22 is planning to make additional data available from</p>
<p style="text-align: right;">Page 246</p> <p>1 tobacco product risks or more exploratory research 2 that investigates the characteristics of different 3 tobacco products.</p> <p>4 So the public health standard that's written 5 into the legislation requires that research is 6 conducted to inform and develop methods to apply 7 that standard. And we don't currently have a set 8 of methods to evaluate modified-risk tobacco 9 product application. So I think this is really a 10 key priority, to develop methods and thinking in 11 that area.</p> <p>12 Third, I think the question of who sets the 13 research agenda has also come up. There are 14 general research needs, as I've said, around 15 developing methods, developing and validating 16 methods for evaluating novel tobacco products. But 17 then, there are also going to be research needs in 18 the context of a particular modified-risk tobacco 19 product application.</p> <p>20 So in thinking about third-party governance, 21 I have to think about who is asking the research 22 questions. And the way this is conducted in the</p>	<p style="text-align: right;">Page 248</p> <p>1 their studies. I think tobacco companies could 2 certainly be encouraged to do the same, to make as 3 much of their own research data available publicly 4 as possible, independent of what other funding and 5 governance structures there may be.</p> <p>6 So I think beginning to put that kind of 7 transparency into practice would be at least a good 8 first step. And at the same time, we need to 9 develop independent research capacity to study 10 modified-risk tobacco products and conduct research 11 in this area, and, in general, to increase our 12 capacity to understand the nature and 13 characteristics of different tobacco products and 14 their effects.</p> <p>15 Really, I know from my place at NIH that 16 there is a relatively small cohort of researchers 17 who are working in this area, studying the tobacco 18 product itself. And we don't have the sort of 19 worldwide network that Duke and others have built 20 up around tobacco product research. And I think 21 it's going to take time and effort to build up that 22 kind of independent expertise. So that's another</p>

<p style="text-align: right;">Page 249</p> <p>1 issue for consideration.</p> <p>2 So thanks. I'll stop there.</p> <p>3 MS. DILLEY: Great. Thanks.</p> <p>4 (Applause.)</p> <p>5 Q&A Session – Abby Dilley</p> <p>6 MS. DILLEY: So we're going to open it up</p> <p>7 for questions for all the panel. David, why don't</p> <p>8 you start us off?</p> <p>9 MR. DOBBINS: Hi. This is Dave Dobbins from</p> <p>10 Legacy. You had mentioned -- and this is for both</p> <p>11 of you. But you had mentioned that the FDA,</p> <p>12 obviously in clinical trials, ultimately approves</p> <p>13 of and understands your design of your study. But</p> <p>14 I take it -- or maybe I'm wrong -- that the FDA has</p> <p>15 never at some point made some sort of declaration</p> <p>16 that the Duke Center is a great center and we can</p> <p>17 rely on the research coming out of it a priori.</p> <p>18 It's studies based on the particular study at hand.</p> <p>19 DR. PETERSON: Right. It's only the NCAA</p> <p>20 tournament that lets us get in at that same</p> <p>21 criteria. No. Sorry.</p> <p>22 MR. DOBBINS: I actually believe that.</p>	<p style="text-align: right;">Page 251</p> <p>1 any results if not sponsored by industry," I guess,</p> <p>2 on the last slide. This is another one of your</p> <p>3 boxes, I think, that maybe you had --</p> <p>4 DR. KUNTZ: This part, I did write.</p> <p>5 MS. DILLEY: Oh, good.</p> <p>6 DR. KUNTZ: I just want to think what the</p> <p>7 context was on that, "Free to discuss any results</p> <p>8 if not sponsored by industry." Well, I think I was</p> <p>9 just making a general statement that when you make</p> <p>10 it publicly available, you allow perspectives</p> <p>11 outside of industry to evaluate the product.</p> <p>12 So, I mean, the general statement is, as</p> <p>13 much as I believe that we act responsibly and try</p> <p>14 to view the data as clean as possible as we can</p> <p>15 with the patient's best interests in mind, we can't</p> <p>16 always make that statement because we have a</p> <p>17 psychological overlay of conflict. This has been</p> <p>18 straightforward, and this has been studied by</p> <p>19 psychologists and sociologists and those forever.</p> <p>20 And the notion is that what we need to do is find</p> <p>21 that forum by which other perspectives can analyze</p> <p>22 the data.</p>
<p style="text-align: right;">Page 250</p> <p>1 DR. PETERSON: Sorry. I couldn't resist. I</p> <p>2 could not resist.</p> <p>3 No. You're absolutely right. I mean, it's</p> <p>4 not a matter of who brings the study to them. I do</p> <p>5 believe there's some credibility that comes perhaps</p> <p>6 with an independent grouping involved in it rather</p> <p>7 than an alternative source. But, truthfully, at</p> <p>8 the end of the day, the design has to meet the</p> <p>9 FDA's rules.</p> <p>10 MR. DOBBINS: And, I mean, I take it -- I</p> <p>11 mean, I'm not trying to cross-examine you, but, I</p> <p>12 mean, I take it that you would agree that that</p> <p>13 credibility has come with performing, again and</p> <p>14 again, reliable studies that the FDA has seen.</p> <p>15 Right. And that's sort of my point.</p> <p>16 MS. DILLEY: We have another one from</p> <p>17 e-mail, so this is to you, Richard. Your last</p> <p>18 slide has a bullet that says, "Free to discuss any</p> <p>19 results if not sponsored by industry." Can you</p> <p>20 explain what you mean by this?</p> <p>21 DR. KUNTZ: Could you say that again?</p> <p>22 MS. DILLEY: Yes. It said, "Free to discuss</p>	<p style="text-align: right;">Page 252</p> <p>1 So I think that's what that statement means,</p> <p>2 is that essentially we will always have a tendency,</p> <p>3 whether we like it or not, to try to shine on the</p> <p>4 benefits more than the risks. Now, all our</p> <p>5 patients -- we take care of other patients as well.</p> <p>6 We'd like to hope that we would never do that, but</p> <p>7 the problem is that nobody is going to trust us in</p> <p>8 that situation. What they will trust us is to have</p> <p>9 a process to be able to get that data for other</p> <p>10 perspectives to look at.</p> <p>11 So I think what it states -- what it means</p> <p>12 is that we want to have people be able to discuss</p> <p>13 and look at data from other perspectives.</p> <p>14 MS. DILLEY: I don't know if we talked about</p> <p>15 this, this morning, but there's a difference</p> <p>16 between conducting the studies and then looking at</p> <p>17 the data separately. The studies were actually</p> <p>18 conducted by Medtronic. Right?</p> <p>19 DR. KUNTZ: That's correct. Yes. Well,</p> <p>20 they're conducted by -- I mean, they're run by</p> <p>21 clinical science.</p> <p>22 MS. DILLEY: Right.</p>

<p style="text-align: right;">Page 253</p> <p>1 DR. KUNTZ: I mean, that's what they're run 2 by. And so the ultimate responsibility of the data 3 comes from the clinical sites, hospitals and 4 clinics that enter the data into the form, which 5 are monitored independently. 6 MS. DILLEY: Questions? If you could, 7 introduce yourself. 8 MR. RUTQVIST: Lars Rutqvist. I have a 9 question to Dr. Kuntz. Could you please elaborate 10 a bit on the nature of the contacts you had with 11 the FDA before you embarked on this impressive 12 effort that you described? Did you get feedback 13 from the FDA? 14 DR. KUNTZ: We immediately informed the FDA. 15 Now, let me give you a little detail about the 16 process here. I will say it wasn't an optimal 17 configuration about how this happened. An 18 individual with well intentions decided to dedicate 19 an entire journal that he was editor of to this 20 issue about our product with 10 or 15 articles. He 21 submitted those articles initially to the New York 22 Times. So we heard about it through the New York</p>	<p style="text-align: right;">Page 255</p> <p>1 matter of fact, that's never been challenged. This 2 data is there. The question is how did it get 3 disseminated through peer-reviewed publications, is 4 my conclusion about how this issue dried. 5 So the FDA was fully informed on this. They 6 had been asked questions at public sessions about 7 this, and they felt that they were anxious to see 8 the results of this independent review. I can't 9 speak to whether or not they did their own internal 10 review on this as well. But I think they probably 11 stand behind their initial review and panel results 12 10 years ago. 13 MR. RUTQVIST: But did they provide feedback 14 on the scope of what you did, or did they come up 15 with suggestions as to extra components of the 16 review? 17 DR. KUNTZ: They were supportive. They were 18 clearly supportive of our process. And while we 19 didn't engage them in the process -- because I 20 think that would be inappropriate both on our part 21 and their part, because they weren't asked to do 22 this -- we let them know what we were going to do</p>
<p style="text-align: right;">Page 254</p> <p>1 Times. 2 This was a Friday afternoon. I was ready to 3 go see my kids play baseball, and I get this call 4 from the New York Times, saying, "Monday or 5 Tuesday, we're going to publish this paper. Here 6 are 15 embargoed papers you should read about. I'm 7 going to call you on Monday and see what your 8 response is." 9 So that was not what I thought was a very 10 optimum way to potentially challenge or go through 11 that. So what I did immediately was inform the FDA 12 to say, look, this is what I just learned. Here 13 are the articles. Take a look at this because I 14 want to make sure that we're clear with you about 15 what these issues are. And while we had informal 16 interactions with the FDA, what we wanted to let 17 them know was our process was going to be to clear 18 this up front here. 19 So I'm sure that they did some internal 20 review of their data. And I don't think anybody's 21 ever challenged the data that we submitted 10 years 22 ago to the Food and Drug Administration. As a</p>	<p style="text-align: right;">Page 256</p> <p>1 with Yale, what our processes were. And they had, 2 obviously, the full opportunity to come back to us 3 and say that they did or didn't agree with that. 4 So I think there's a tacit agreement that this was 5 probably a good process. 6 MS. DILLEY: So you weren't looking for 7 approval. You were looking more for red flags. 8 DR. KUNTZ: This is all novel. This is new. 9 Nobody's ever done it before. 10 MS. DILLEY: Right, right. 11 DR. KUNTZ: So our issue was to make sure 12 that we were just informing as many people as we 13 could about what we were doing, and it seemed to be 14 consistent with what their goals were. 15 MR. RUTQVIST: Thank you. 16 MS. DILLEY: Other questions? 17 MS. LEE: I'm Monica Lee from JTI. Perhaps 18 it's more general to all the panel members, if 19 that's okay. I was a bit surprised because we 20 talked about types of research, but if you focus on 21 MRTP, there is already draft guidance out there. 22 The IOM report came out in 2011 and, as everybody</p>

<p style="text-align: right;">Page 257</p> <p>1 knows, about several months later, FDA issued draft 2 guidance on MRTP and what kind of scientific 3 evidences. And I believe a lot of recommendations 4 from IOM in terms of scientific evidence -- for 5 example, importance of clinical 6 studies -- reflected in the draft guidance. But 7 the terminology of third-party governance I believe 8 is missing. However, some components that I think 9 we all talked about today, some essence seems to be 10 there.</p> <p>11 For example, the sensitive subpopulation 12 testing FDA recommends discussing before the 13 conduct. And at the end of study, all the data in 14 the report would go through mandatory review by 15 TPSAC, as well as released to the public.</p> <p>16 So that is quite a lot of governance 17 checkpoints in the draft guidance, and I was 18 wondering how the panel member feels about those 19 checkpoints are still not adequate. We still need 20 another third party. Or not?</p> <p>21 MS. DILLEY: You're asking to their 22 particular products and the relevance for their</p>	<p style="text-align: right;">Page 259</p> <p>1 points. First of all, that doesn't say what the 2 methods are that should be used to conduct that 3 research, exactly what tests need to be done to 4 develop data to submit as part of an MRTP 5 application. The reason is because I think, 6 scientifically, we're not quite there yet. We 7 don't have, say, a battery of tests that we can 8 apply to say whether a product meets the standards 9 for an MRTP or not. I think that's something that 10 requires scientific study and investigation to 11 develop. I mean, I can't speak for FDA, but I 12 expect that that may be their intent.</p> <p>13 Secondly, as to why we need a third-party 14 governance, the third-party governance is not so 15 much directed at evaluating the methods. I think 16 it's really ultimately for FDA to decide what 17 evidence is adequate to meet the requirements. But 18 the third party is more to oversee the conduct of 19 research, and I think that's the context we've been 20 talking about so far, is that it would be -- if 21 such a mechanism were to be established, it would 22 be ensured that the data is collected in a way that</p>
<p style="text-align: right;">Page 258</p> <p>1 governance, or are you talking about MRTP? 2 MS. LEE: I'm talking about MRTP. If the 3 essence of a third party is to make sure 4 transparency, reproducibility, all that, it has to 5 be reserved, is the checkpoint currently the draft 6 guidance; it is something relevant to meeting of 7 needs of the third party? Or are we talking 8 certain studies or certain checkpoints, that 9 currently presented as a draft guidance, we have to 10 use as a third party? Is that their 11 recommendation?</p> <p>12 So it's just a general question to the panel 13 members, I guess.</p> <p>14 MS. DILLEY: Richard and Eric, I don't know 15 if you want to respond to MRTPs in particular, 16 because that's not your area of expertise. But, 17 Mark, if you want to do that, and you're also 18 obviously welcome to comment on it.</p> <p>19 DR. PARASCANDOLA: Yes. I can respond 20 first. So, yes. There is FDA guidance on what 21 kinds of evidence maybe would be looked at in 22 evaluating an MRTP application. But a couple of</p>	<p style="text-align: right;">Page 260</p> <p>1 it can be credible and reliable.</p> <p>2 MS. LEE: Just a quick comment. If you're 3 talking scientific integrity, in many points, I 4 think for example GRP, GMP, as well as IRB, has 5 been already addressed in the draft guidance. So 6 that's what I'm trying to understand; what 7 additional benefit or we are lacking in the draft 8 guidance. Because the draft guidance is not just 9 the type of study. It's how the study has to be 10 conducted, how the public health standard has been 11 met. And I believe you must have read it. You 12 must have read it.</p> <p>13 So I'm trying to understand, reconcile, the 14 draft guidance, what FDA is recommending versus 15 what additional guidance is necessary to meet the 16 goal of the public health standard. That's it for 17 me.</p> <p>18 DR. PARASCANDOLA: Well, again, I can't 19 speak for FDA, but speaking from the scientific 20 community, I think there are still gaps. And as I 21 said before, I don't think we have a series of 22 methods that are well-accepted across the</p>

<p style="text-align: right;">Page 261</p> <p>1 scientific community to evaluate whether a 2 potential modified-risk tobacco product really is a 3 modified-risk tobacco product or not. 4 So far, the requirements that have been 5 suggested are very general. I don't know that we 6 have worked out all the methods for how we get 7 there yet. 8 MS. DILLEY: So I have an e-mail question. 9 "In your section on roles and 10 responsibilities, Richard, of the different 11 sectors, listed under academic reference, it said 12 that, 'Academics are free to discuss any results if 13 not sponsored by industry.' 14 "By contrast, Eric said that at DCRI, 15 sponsors provide cash, but once DCRI gathers that 16 data, they have freedom to do what they want with 17 it. 18 "With MRTP, does Mark think --" 19 (Laughter.) 20 MS. DILLEY: If there were two other panel 21 members, we'd have questions for them. But "Does 22 Mark think that the DCRI approach makes more sense</p>	<p style="text-align: right;">Page 263</p> <p>1 MS. DILLEY: Based on two 15-minute 2 presentations, I don't know why not. 3 DR. PARASCANDOLA: Yes. 4 MS. DILLEY: No. I'm just kidding. 5 DR. PETERSON: May I comment just a little 6 bit more? 7 MS. DILLEY: Yes. 8 DR. PETERSON: I mean, I think the concern 9 is that, is there ways in which potentially studies 10 could be done and the information not be available 11 in a way that could potentially have meaningful 12 ramifications on health that wouldn't be released 13 in some other fashion. And I think there's lots of 14 different ways to protect it. And you've heard 15 multiple parts of that -- Camel now -- through 16 these presentations. 17 One of them even begins with the 18 clinicaltrials.gov kind of thing, registering all 19 studies that are going forth. At least you have a 20 record of that. As you go further, you get to a 21 point of, yes, if the investigators who did the 22 study have access to the data and can publish it in</p>
<p style="text-align: right;">Page 262</p> <p>1 or would the Medtronic view be acceptable?" 2 So just trying to think of those 3 different -- and I don't know acceptable based on 4 what, but it's a question to you, Mark, ultimately, 5 in terms of thinking about the different elements 6 of those models. 7 DR. PARASCANDOLA: Well, I don't want to 8 pick favorites among my fellow panel members. 9 Well, yes. I don't think I can -- I mean, I 10 think the purpose, as I understand it, to hear 11 about these others models, was to provide us some 12 context for different mechanisms for providing 13 research governance. But I think, as we've heard 14 this morning, there are still a lot of unique 15 issues around tobacco products research that are 16 very different. And some of those concerns -- it 17 wasn't the intent for Duke Research Center or for 18 Medtronic to address those issues. They had their 19 own set of concerns they were addressing. 20 So I think this is informative, but I 21 wouldn't say that either model is going to be the 22 one that we need for tobacco products research.</p>	<p style="text-align: right;">Page 264</p> <p>1 a way that's fair and impartial, that's a very good 2 check. 3 The third level is the FDA, obviously, when 4 it goes to market has access to all the totality of 5 the data and provides a regulatory review of the 6 information, as was again described on how products 7 come. 8 Then the final thing is looking at both the 9 peer-review process. And then ultimately perhaps 10 the most extreme, as what Medtronic is undergoing 11 now, which is putting out the totality of the data 12 for a systematic review. And I think that those 13 are all remarkable but complimentary checks to try 14 to get better access. 15 MS. DILLEY: You don't necessarily have to 16 pick one best one. There are different ways of 17 putting checks in the system. So I think that's a 18 great way to lay it out. 19 Yes? 20 DR. KUNTZ: We might want to just show that 21 there are three basic models to collect data. And 22 maybe the analogy could go over to tobacco. But</p>

<p style="text-align: right;">Page 265</p> <p>1 one is that a company like ours will both write the 2 initial protocol approved by the Food and Drug 3 Administration, conduct the study, do the analysis, 4 and submit that to the FDA for approval. And 5 that's probably our main approach. 6 The second is that we would hire Duke to run 7 the study and collect the data. And we would, 8 together, write the protocol and work with the FDA. 9 And then they would do the analysis and submit it 10 to them. 11 A third would be that -- which was never 12 done, I don't think, in the industry, is that 13 someone like Duke would actually do the study 14 independently of the company and evaluate our 15 product somehow. That model has never been 16 developed, I know, especially in the pre-market. 17 I think what you'll find is that all three 18 of those models have very traceable and monitorable 19 processes, because the FDA is so rigorous with 20 respect to how they set up stuff. The difference 21 is going to be in the analysis and the emphasis. 22 And that's where I think we have to just make sure</p>	<p style="text-align: right;">Page 267</p> <p>1 here. We had another one back here, and then up 2 here to David. 3 We've got time, David. 4 MR. ROULET: Steve Roulet from Philip 5 Morris, International and my question is to Mark. 6 You were talking about global expertise that the 7 FDA might benefit from. Could you be a little bit 8 more explicit, maybe, knowing that the FDA is the 9 only regulator so far that has created guidance for 10 MRTP? Which area could they benefit from 11 international knowledge? 12 DR. PARASCANDOLA: Well, I think there are 13 many areas where they could benefit from. Although 14 there's a large network of people who do research 15 in tobacco control, treatment of tobacco dependence 16 and this sort of area, there are relatively few 17 really who study the characteristics of tobacco 18 products, say tobacco product chemistry, the 19 toxicology of tobacco exposure, as well as the 20 kinds of clinical evaluations that would need to be 21 done, and all the population studies that would 22 need to be done to meet the public health</p>
<p style="text-align: right;">Page 266</p> <p>1 that everybody's aware that that's where the 2 promise -- we hope that we would be able, in all 3 three of those models, be able to demonstrate that 4 we could trace, through monitoring the data 5 validity, the source documentation. And all the 6 monitoring processes with all three models have to 7 be meeting certain high standards, and they are 8 high standards. 9 But when we get down to understanding what 10 to emphasize, and what not to emphasize, and what 11 to look at with respect to how we report adverse 12 events, and so on, is I think where the public 13 comes in, because then everybody can view this 14 themselves and analyze this. 15 So I don't know if that helps develop the 16 structure a little bit more, but if we get into a 17 situation where we have more rigor with respect to 18 how the data is collected, then you have a great 19 vehicle, so it doesn't really matter who's doing 20 it. It's really about getting the data available 21 for analytical purposes. 22 MS. DILLEY: Thank you. Let me go back</p>	<p style="text-align: right;">Page 268</p> <p>1 standards. 2 So I think there's a whole array of -- and I 3 can enumerate them all. But there's certainly an 4 array of disciplines that would need to be 5 involved. And right now, there is -- yes, I think 6 the capacity is still limited for research in that 7 area. Certainly, we hope to see that change, and I 8 know NCI is funding more research in this area, and 9 I think it's important to develop that independent 10 capacity. 11 MS. DILLEY: I thought we had a hand back 12 here. 13 MR. WALKER: Jeff Walker, Altria Client 14 Services. 15 Dr. Kuntz, I have a question for you. I 16 know Medtronic to be a very thoughtful 17 organization. When you had this opportunity 18 presented to you on Friday afternoon, you had a 19 number of different courses that you could have 20 taken. You mentioned notifying the FDA. 21 The question was, by sending this out into 22 sort of a different construct that hasn't been</p>

<p style="text-align: right;">Page 269</p> <p>1 tried before, how will you think about what to do 2 if the results come back mixed. Adverse? And 3 what's the role of the FDA? And because they 4 regulate your product, does this take the decision 5 away from the agency and gives it now to Yale? 6 Gives it to Medtronic? How does the FDA play back 7 into the role in going forward? 8 DR. KUNTZ: It's a good question, but I 9 don't know if it's much different than a normal 10 post-market study would have. So say, for example, 11 the more common approach is that we do a 12 post-market study looking at the long-term duration 13 or benefits of an implantable device, and we find 14 that, in fact, there are some negative aspects as 15 opposed to the positive that we had hoped for. But 16 then we work with the FDA to determine what the 17 best course of action is. 18 It's our responsibility to make that initial 19 communication with the FDA, and to be as quick as 20 possible, and then to get an initial gauge, is 21 there something we need to do tonight? Is there 22 something we can do in a week or so? And what are</p>	<p style="text-align: right;">Page 271</p> <p>1 report, but those are the kind of checks we put in 2 place to make sure that we could be responsible in 3 this process going forward. 4 So at the end of the day, we're going to 5 carefully review the results. We are putting our 6 trust in the systematic reviewers and in others, 7 that they're going to come up with probably the 8 best analysis of our results. We may have the 9 opportunity to challenge some of those results, but 10 the key is, it's going to be out there in public. 11 And that's what we want to do. And then I think 12 we'll work with the FDA to say, "Are there 13 modifications to the label we need to make or 14 actions we have to take if we find something that's 15 detrimental to the public?" 16 MR. WALKER: That's great. Just as a quick 17 clarification, then, you're using it as a 18 post-market study. But in some ways, you're 19 actually using it in a governance setting. It 20 seems to me there's almost a decision-making, a 21 question about decisions that you're offering up to 22 the independent institutions.</p>
<p style="text-align: right;">Page 270</p> <p>1 the issues? And then appropriately act. 2 I think we'll follow that same model 3 because, ultimately -- and, by the way, I just want 4 to make sure that, in this process, Yale and others 5 who have been looking at the data and the 6 intermediary products that have led -- because the 7 final peer reviews are not finished yet; they'll be 8 published. But they've seen the data on the way. 9 We have asked them and others that if there 10 are issues that you're concerned about immediately, 11 to pull the chain on the chain, to stop it, because 12 we want to make sure that this isn't something 13 where we find out there's some real terrible thing 14 that took two years for us to figure out because 15 it's a long, lengthy process. 16 So we've been very clear about that, both 17 the FDA and also to Yale, that if anybody sees 18 things where they think there has to be immediate 19 action, that we should be informed, but we haven't 20 seen that yet. 21 Now, that doesn't necessarily mean that 22 we're going to have a really bright or less bright</p>	<p style="text-align: right;">Page 272</p> <p>1 So I guess, why wouldn't this process have 2 been run through the FDA as a secondary analysis, 3 as a post-market study? I guess I'm struggling to 4 understand why the new construct, when there's an 5 available construct, could have been used. 6 DR. KUNTZ: Well, I think it depends on what 7 the strength of the initial evidence was compared 8 to how the FDA felt with the existing data. And 9 it's relatively novel. I don't know. This 10 experience might turn it into something where they 11 write guidelines that they want to be more involved 12 with, anything that comes up with this before. 13 It's not unusual for products to be 14 challenged on the market. That happens all the 15 time. What happened here was, it was a very large 16 effort to challenge it, and we responded back with 17 an independent report. And I think that -- I can't 18 speak for the FDA at all, so I don't even want to 19 venture for that. But my guess is that they were 20 coupled with our process. 21 MS. DILLEY: David, did you have a question? 22 MR. DOBBINS: Just an observation. Just</p>

<p style="text-align: right;">Page 273</p> <p>1 listening to the two of you, these are interesting 2 experiences. But I don't know that they're really 3 responsive to the IOM recommendation, because in 4 neither case do we have research -- and, indeed, 5 it's sort of been, a priori, stamped, it's good. 6 What I think is more interesting here and 7 maybe more informative to the task is developing 8 standards for data transparency and collection. 9 And that leads me to a question. And I think it's 10 a bit of follow-up to the last question. 11 I mean, I take it -- and I'm not trying to 12 be unfair, so you can oppose me, but what motivated 13 you to do this very public, high-profile, Yale-led 14 intervention is the fact that you in some degree 15 were put into crisis communication mode by being 16 blindsided by a gigantic effort that's going to be 17 reported in the New York Times. 18 I do think it's interesting, and what I'm 19 interested in is what kind of model this could 20 gather for confidence in data analysis, so less 21 than I'm interested in what your experience is like 22 for third-party governance, because it really isn't</p>	<p style="text-align: right;">Page 275</p> <p>1 That was my response. And that's why we said we 2 need to have somebody else independently review 3 this. 4 I feel pretty strong about the data we have 5 because I've looked at the data. I think it 6 actually is pretty valid, with the FDA and 7 everything else. But, again, if there was any 8 chance that what I was comfortable with, in 9 normally how we generate knowledge, might have 10 fallen through the cracks in other areas that I 11 wasn't comfortable, that's the main reason we went 12 to a third party, and we'll see what they say. 13 MS. DILLEY: I guess a follow on to that, a 14 question about -- and you may have mentioned this 15 earlier when we were chatting, is the side 16 implications of researchers, so putting data out 17 there for the research centers and some of the 18 complications. I mean, Eric could raise some 19 issues around that in terms of people feeling that 20 they can go into this area of research, and if 21 other data are released, does that have a negative? 22 DR. KUNTZ: Yes. The experience I've had so</p>
<p style="text-align: right;">Page 274</p> <p>1 a third-party governance situation. 2 MS. DILLEY: That's the transparency issue. 3 DR. KUNTZ: Right. This was a question that 4 we reacted to this as a response, so this was not a 5 proactive approach. I will say, though, that I am 6 very comfortable with the processes throughout our 7 company. I'm a cardiologist, and the cardiology 8 arena -- Eric's a cardiologist. I mean, we 9 probably have more experience with structured 10 evidence than almost every other field of medicine, 11 and I think most people kind of recognize that. 12 I'm not quite sure why that is, but it's 13 true; we have a lot of cardiac data. The company 14 Medtronic is heavily based in cardiac outcomes, so 15 we have very deep and, I think, responsive clinical 16 studies in the cardiac arena. 17 In looking at other areas like orthopedics 18 and others like that, where the history of evidence 19 building is mounting but not as strong as it is in 20 cardiology, what was a shock to me was, could it be 21 possible that we actually have information that 22 wasn't as clear as I'm used to in other areas.</p>	<p style="text-align: right;">Page 276</p> <p>1 far is that, in trying to paint the world as a 2 transparent world, where industry who -- if you 3 look at the breakdown of studies, it's still mainly 4 dominant in industry, especially in the medical 5 arena. An index people use is if you look at the 6 last 10 years of the New England Journal of 7 Medicine, about 50 percent of the studies published 8 in that prestigious journal are industry sponsored. 9 The next highest group is the VA, which is about 15 10 percent, then NIH, and so on. 11 So industry still provides a lot of the 12 studies and, if we say, let's move to a world where 13 industry does its regulatory requirement and makes 14 the data publicly available, I think we can get 15 there. 16 It's often complicated for academia because 17 if you're -- and Eric will speak to this with more 18 authority than I will. But if you're an assistant 19 professor who's applied three times to the NIH to 20 get a grant, it's taken you three or four years, 21 then you have done all the hard work of getting 22 sites on board, and writing the protocol, and doing</p>

<p style="text-align: right;">Page 277</p> <p>1 the analysis, and yelling at people for not 2 enrolling, and doing all that process for three or 3 four years, and you got the final results, do you 4 want to give that data up immediately? All the 5 hard work you put into it, and have your 6 colleagues, who didn't do anything, sit on the side 7 and say, "I'll take that data set. Let me write 8 the paper really quickly." That becomes a race as 9 to who can publish, because the world of academia 10 rewards publications. 11 So there is going to be, even from the 12 academic side, a zone of protection. And maybe 13 that zone is a year, which actually would be a good 14 thing because it would force people to publish 15 quicker than they are right now. But I think that 16 there are going to be a lot of consequences of 17 trying to push this envelope of transparency that 18 might not be apparent up front as to who's going to 19 be pushing back and who's not. 20 MS. DILLEY: Eric, are you wincing? 21 DR. PETERSON: No, no, no. I would actually 22 just fully agree. I think that the other model</p>	<p style="text-align: right;">Page 279</p> <p>1 don't know. Is your question to Eric? 2 MR. WILCOX: No. You can catch your – 3 (Laughter.) 4 MS. DILLEY: Thank you very much, by the 5 way. 6 MR. WILCOX: Neil Wilcox, Lorillard Tobacco 7 Company. It's a very interesting discussion, and I 8 appreciate it. In response to the question about 9 the draft guidance on MRTPs that is currently 10 there, Dr. Parascandola said a couple times that 11 the methods simply aren't out there yet or haven't 12 been recognized by FDA as to what might be used to 13 approve an MRTP. 14 I guess I have a statement, and then maybe 15 somewhere in here, maybe a question. 16 MS. DILLEY: Excellent. 17 MR. WILCOX: So bear with me. I will try to 18 not be inarticulate. 19 As I understand it, historically speaking, 20 when FDA is presented a submission for product 21 approval, they don't tell the sponsor -- albeit a 22 drug company, a tobacco company, or academia,</p>
<p style="text-align: right;">Page 278</p> <p>1 that's developing similar to this NIH is even 2 pushing a window around data that's sponsored by 3 NIH being available then to the public as well. So 4 I think it's a moving target of how long we'll have 5 protection, even under our rights to publish, to 6 try to keep our resumes look good. 7 I do apologize. Is there any other final 8 questions that have to be directed my way? I've 9 got, unfortunately, transportation outside. 10 MS. DILLEY: I have one question, an e-mail 11 question, and then I know the gentleman back there 12 had a question. 13 Would Duke be able, under its current 14 structure, to take tobacco industry funds? 15 DR. PETERSON: I don't know, to be honest. 16 We've never tried to do that. I guess Dr. Rose 17 could probably speak to Duke. As a Duke 18 investigator, you were able to do it. 19 MS. DILLEY: Yes? 20 MR. ROSE: No. I don't know of any official 21 public policy that says to the contrary. 22 MS. DILLEY: A gentleman back here, and I</p>	<p style="text-align: right;">Page 280</p> <p>1 whoever may be submitting the application -- they 2 don't tell the sponsor what methods are to be used. 3 Instead, it's up to the sponsor to say this is my 4 claim. This is a modified-risk product, this 5 tobacco product. This is a modified exposure 6 tobacco product, whatever their claim may be. Then 7 it's up to the sponsor to say these are the methods 8 that we're going to use to substantiate our claim. 9 The operative word here is claim. What is a 10 claim for this MRTP? And then it's up to the 11 sponsor, once again, to say these are the exposure 12 characteristics, for instance, the portal of entry, 13 the dose including frequency, duration, and so 14 forth. 15 Then FDA would review the protocol and the 16 results of the studies that are put forth by the 17 sponsor and either agree or disagree that they have 18 substantiated the product. 19 So with that rather lengthy introduction, my 20 question is to Mark, under what circumstances do we 21 expect FDA to come up with a group of methods to be 22 used to substantiate MRTPs? And we may need David</p>

<p style="text-align: right;">Page 281</p> <p>1 Ashley to weigh in here.</p> <p>2 MS. DILLEY: You are not going to get David</p> <p>3 (inaudible – off mic.)</p> <p>4 MR. WILCOX: I know. I'm just trying to get</p> <p>5 David involved.</p> <p>6 DR. PARASCANDOLA: Well, I guess I would</p> <p>7 say -- again, I can't speak for FDA. I certainly</p> <p>8 didn't intend to imply that FDA hadn't recognized</p> <p>9 methods that are out there, because that's for FDA</p> <p>10 to determine what methods they're going to</p> <p>11 recognize. But I am speaking from the point of</p> <p>12 view of the science. And I think among scientists</p> <p>13 who work in this area, at least public health</p> <p>14 scientists who work independently of the tobacco</p> <p>15 industry, I don't think there is agreement on a set</p> <p>16 of methods that would sort of provide a road to</p> <p>17 approval of a modified-risk tobacco claim.</p> <p>18 That's not to say those methods can't be</p> <p>19 developed, but I don't think there is a consensus</p> <p>20 around, say, a set of methods that could do that</p> <p>21 currently. And I think this is an area that we're</p> <p>22 continuing to support research in, and I think is a</p>	<p style="text-align: right;">Page 283</p> <p>1 drawing stages up front here, but they have at</p> <p>2 least announced intentions to move in that</p> <p>3 direction.</p> <p>4 We haven't seen anybody in the device side</p> <p>5 do that yet. That doesn't necessarily mean they</p> <p>6 don't have plans to do that. I just haven't seen</p> <p>7 it. But I think what's going on is that -- I would</p> <p>8 say that, from a generic perspective, a lot of</p> <p>9 people kind of took a deep breath when they heard</p> <p>10 what we were doing. And there were some initial</p> <p>11 feedbacks saying this is the wrong thing to do up</p> <p>12 front. But I think that as time goes on, people</p> <p>13 start to see that this horse has left the barn.</p> <p>14 We're going to live in a transparent world whether</p> <p>15 we like it or not.</p> <p>16 One way that I've always talked about it is</p> <p>17 in addition to democratizing data, which I think is</p> <p>18 really important, a smart company will realize</p> <p>19 they've got to do this anyway because data access</p> <p>20 is going to be available to anybody sooner or</p> <p>21 later.</p> <p>22</p>
<p style="text-align: right;">Page 282</p> <p>1 high priority to develop for the future.</p> <p>2 MS. DILLEY: We have another e-mail question</p> <p>3 for you, Richard. And I think you touched on this</p> <p>4 a little bit.</p> <p>5 "How have other devices or companies reacted</p> <p>6 to the process you've described? Do you see other</p> <p>7 companies following or will they wait to see the</p> <p>8 outcome?" I think you said, yes, they're kind of</p> <p>9 waiting, but you may have talked with your</p> <p>10 colleagues.</p> <p>11 "Are planning to work with Yale for</p> <p>12 re-analysis, the analyses of other products."</p> <p>13 DR. KUNTZ: I can tell you, they're on the</p> <p>14 sidelines, watching, and they're anxious. I think</p> <p>15 we've had more positive response from the drug</p> <p>16 companies. So I have done this presentation for</p> <p>17 the Institute of Medicine at a transparency</p> <p>18 workshop, where companies like Merck and GSK and</p> <p>19 others have outlined initial plans for data</p> <p>20 transparency.</p> <p>21 Some of them are consistent with what we</p> <p>22 have. I think they are still somewhat in the</p>	<p style="text-align: right;">Page 284</p> <p>1 So because of these things, I would rather</p> <p>2 have a more formal way, where they get the right</p> <p>3 data, as opposed to trying to hack some information</p> <p>4 and say they're going to get the data some other</p> <p>5 way. So when we think about all those issues up</p> <p>6 front here, this is, I think, a reality that slowly</p> <p>7 people are kind of realizing.</p> <p>8 MS. DILLEY: Just from the technology, what</p> <p>9 was your timeline? Do you know what the timeline</p> <p>10 is?</p> <p>11 DR. KUNTZ: Yes. We have a mixture of a</p> <p>12 business process where people in our company get</p> <p>13 rewarded to make sure that they hit milestones</p> <p>14 mixed with an academic process, where they don't</p> <p>15 have those same incentives. And that's things like</p> <p>16 the publication process, which is totally relevant</p> <p>17 to how they do things.</p> <p>18 So when we look at the peer-review</p> <p>19 publication process, what drives those things is</p> <p>20 how long reviewers take to review stuff, and</p> <p>21 whether they need to go back for revisions, and so</p> <p>22 on. So anyway, that process is independent, and it</p>

<p style="text-align: right;">Page 285</p> <p>1 looks like we're going to get our publications out 2 in Annals in June.</p> <p>3 MS. DILLEY: In June? So not too long from 4 now. Yes. Question over here, then Joanna.</p> <p>5 MR. OGDEN: Mike Ogden with RAI Services. I 6 think, Dr. Kuntz, this question is for you. And 7 you partially addressed it in an answer maybe 5 or 8 10 minutes ago. But if I understood what you said 9 in your presentation, you had a dozen or 14 or so 10 studies that had all been conducted by you as the 11 sponsor, both pre-market and post-market.</p> <p>12 I presume, safely I'm sure, that all of 13 those were done with full transparency to FDA. And 14 then after the fact, so to speak, some of those 15 conclusions were perhaps questions in terms of the 16 risk-benefit ratio, based on a greater weight of 17 evidence.</p> <p>18 Imagine a world where perhaps you as the 19 sponsor had done a half a dozen studies 20 pre-market/post-market, and then some other studies 21 came to light funded by, perhaps, academicians, 22 perhaps by even your competition, that sort of now</p>	<p style="text-align: right;">Page 287</p> <p>1 So the way you talked about that scenario, 2 the first thing would be, yes, knowledge is 3 important to generate. If there's more data that's 4 quality, of course we want to be able to get that 5 data and combine it; whether people feel 6 comfortable giving that data to us for us to 7 combine it, or if we go to a third party so we can 8 work it out.</p> <p>9 But if anybody has any relevant data about 10 our products, that's important to see it. And 11 we've seen that with health plans. Certain health 12 plans that have their own data have shared their 13 data with us and also with the public. So, I mean, 14 the idea of having competitors go after us to show 15 that we're not there is just something we have to 16 consider. But the answer is, if the methods are 17 right, then we want to know what the results are. 18 If the methods are biased, then we want to point 19 out the bias.</p> <p>20 MS. DILLEY: Joanna, do you have a question? 21 DR. COHEN: Yes. Just a question of 22 clarification. So I think you said you haven't</p>
<p style="text-align: right;">Page 286</p> <p>1 look like an altered risk-to-benefit ratio.</p> <p>2 In your model with Yale, would you advocate 3 that all of those studies be made available in the 4 full, transparent way to fully address the issue?</p> <p>5 DR. KUNTZ: Yes. The answer is yes. If the 6 data -- if the other studies -- we can speak about 7 the quality of the studies that we sponsor and 8 contract. So we'd have to do a quality check to 9 make sure that those other studies are out there, 10 and there are a lot of studies that aren't done 11 with good quality.</p> <p>12 What I mean by poor quality is, the most 13 common offenders of poor quality are normalization 14 and standardization of the endpoints, the rigor of 15 which the data was collected, and the 16 ascertainment, which is the missing data. And 17 missing data is always missing at bias. It's never 18 at random.</p> <p>19 So we put a lot of effort to make sure that 20 we collect everything. And some studies that don't 21 have that rigor don't collect that, and you get the 22 wrong answer.</p>	<p style="text-align: right;">Page 288</p> <p>1 seen the results yet of the systematic review.</p> <p>2 DR. KUNTZ: We have seen a preliminary 3 result of the systematic review, yes.</p> <p>4 DR. COHEN: But not the paper that's been 5 submitted?</p> <p>6 DR. KUNTZ: No.</p> <p>7 DR. COHEN: Are you intending to?</p> <p>8 DR. KUNTZ: That's a good question. We 9 probably will. And, again, I don't want to talk 10 about too much insider, but we have asked for maybe 11 a few-day buffer because we're going to be hit by 12 all the press, and we want to be able to prepare 13 what we're going to say. So that part, I think, is 14 going to be something that may give us an embargo, 15 48 hours or something, to see that.</p> <p>16 We've also talked about whether or 17 not -- there were some issues or ideas raised about 18 myself writing an editorial in that journal from 19 the perspective of what it was like for me to go 20 through this process and the company as a whole, 21 which would mean that I would get access to the 22 articles, obviously, if I was going to write an</p>

<p style="text-align: right;">Page 289</p> <p>1 editorial before then. But that decision has not 2 been made, and it may not be made. 3 So those are the only two opportunities that 4 we would have to be able to look at those 5 manuscripts before they get submitted. 6 DR. COHEN: So I was just trying to put two 7 and two together because you had said you hadn't 8 seen the results, but on the other hand, the papers 9 are going to be published in a journal. So the 10 paper has been submitted. It's in press. Right? 11 The systematic review is in press? 12 DR. KUNTZ: Yes. So just to be really 13 clear, in the contract that we agreed with Yale 14 was, the preliminary results of the systematic 15 review, and actually the first drafts of the 16 manuscripts, we would have access to, to be able to 17 send back comments. 18 So what we want to do was to make sure 19 that -- to protect the systematic reviewers, since 20 we knew the data intimately, that if we saw some 21 fundamental problems, we didn't want to embarrass 22 them by having them coming back and saying, "They</p>	<p style="text-align: right;">Page 291</p> <p>1 publication. 2 DR. KUNTZ: They were accepted before we 3 even did the project, so the idea was that -- 4 DR. COHEN: So that's what I'm trying to get 5 at. So they were accepted before the work was 6 done. I'm trying to understand that. 7 DR. KUNTZ: Yes. So I think what we had was 8 an agreement. I mean, obviously, if the papers are 9 terrible, the publisher is not going to -- the 10 editor is not going to put it out there. But the 11 idea was that we had worked with -- and, again, I 12 give all credit to Christine Laine at the Annals 13 and others to say that this is a novel approach 14 about the data transparency process and so on. And 15 we wanted to make sure that we could come out in a 16 systematic way to explain this story that made 17 sense. 18 What we thought would be good is to have 19 both publications from these different groups come 20 out in a prestigious tier-one journal. And our 21 first choice was to talk to Annals. And when we 22 told them about this process, they said, "Yes, we</p>
<p style="text-align: right;">Page 290</p> <p>1 did the analysis wrong." 2 Now, the chances of them doing the analysis 3 wrong is probably pretty low. But both parties 4 agreed that we would look on the data on the 5 preliminary. We would send our comments back. The 6 Yale team would actually make comments on that, 7 just so the systematic reviewers, when they wrote 8 their final drafts and their manuscripts to be 9 submitted to the journal, would get viewpoints from 10 everybody. And there's no obligation they had to 11 even read our stuff, but we gave it to them. 12 That's the only time I actually got to see that 13 data. 14 Now, the manuscripts have gone through peer 15 review. I'm not seeing any of the peer-review 16 responses, any of the relationships between the 17 reviewers, and what revisions are being made. We 18 don't get privy to that. And we haven't seen any 19 of the revisions of the systematic reviews, which 20 will come out as well. So our only insight was on 21 the first round. 22 DR. COHEN: But they have been accepted for</p>	<p style="text-align: right;">Page 292</p> <p>1 would be happy to do that," just like other 2 journals may negotiate. They would be the primary 3 group that would publish this. 4 Now, I guess what I don't know is, if the 5 reviewers feel like the quality of the work isn't 6 worthy of publication, well, then they don't 7 publish it. But my guess is, with these two 8 standing systematic reviewers, that's not going to 9 be an issue about the quality of the stuff, 10 especially if they follow the peer-review process. 11 So this is more about -- and I think also 12 with that idea was not only were the results of the 13 study going to be important for Annals, but also 14 the editorials that would surround that, comments 15 about data transparency, the journey, and all that 16 kind of stuff was I think what they are going to 17 try to focus that issue on. 18 MS. DILLEY: So that's the study -- it's the 19 analysis itself, but it's also the fact that this 20 is a new model. 21 DR. KUNTZ: Yes. And, again, I don't want 22 to speak for the Annals because I'm two or three</p>

<p style="text-align: right;">Page 293</p> <p>1 degrees removed on this process. But it's been a 2 very positive relationship by them at least trying 3 to help push this journey further. In all the 4 comments I made about what they did, the details 5 might be wrong, but that's my understanding. 6 MS. DILLEY: So yes, Mark? 7 DR. PARASCANDOLA: I just wanted to ask a 8 follow-up question, too, because I think this is a 9 great example. So when you talk about the data 10 being made available, obviously it was made to 11 those who are doing the analysis. But I thought 12 you had referred also to data being made more 13 publicly available once it's been de-identified, so 14 I guess I was curious how that process works. 15 DR. KUNTZ: So we have committed to making 16 the data publicly available. We haven't committed 17 on the methodology yet. And that's still a process 18 ongoing. And we're trying to time it for the 19 announcement of the process, when the publications 20 come out. So we're actually in the throes of 21 trying to understand this process. 22 I think we all agreed that the first</p>	<p style="text-align: right;">Page 295</p> <p>1 And so patients depend on having these products out 2 there. And when we pull products off the market, 3 we get a lot of input from patients that say, "We 4 needed that product. You're pulling away from the 5 market. Why is that?" So we also want to assure 6 that any benefits of the products we make for 7 patients who can get there also don't get thwarted 8 by irresponsible analysis. 9 So it's a big burden for us, for 10 responsibility, to figure out how to navigate 11 through this, to be both publicly responsible, but 12 also not go too overboard that we end up with a 13 situation that might harm people because of lack of 14 access to a product that might be helpful to them 15 as well. 16 Again, this is, I think, something that's 17 fully understood by these independent groups that 18 are working with us. And they are trying to work 19 through that process. And there's no formula. 20 There's no roadmap for this. 21 MS. DILLEY: We have time for maybe one or 22 two more questions, if there are any. We weren't</p>
<p style="text-align: right;">Page 294</p> <p>1 time -- industry has never done this. There's 2 never been, in the history of drugs or devices in 3 biologics, anyone who's made patient-level data 4 available to the public. And there is a lot of 5 concerns about this process. So we want to make 6 sure that we move in a measured pace and understand 7 that process. 8 So I can tell you, it won't be a spreadsheet 9 put on the Web that people can get with every piece 10 of data. We will have a process which is very 11 fair. It will be completely controlled by Yale. 12 It won't be controlled by Medtronic. And it will 13 be done with the best intentions by those 14 individuals I talked about on the steering 15 committee, and others, to make sure that 16 responsible questions are being asked and 17 responsible research is being done, regardless of 18 whether it means anything good or bad for 19 Medtronic. 20 We talk a lot about industry's bad views and 21 not reporting adverse events. We actually make 22 products that actually help patients, too, as well.</p>	<p style="text-align: right;">Page 296</p> <p>1 going to keep you up here a whole other hour, 2 Richard. Don't worry. Mark. 3 So any more? Any online? One more. 4 MR. DILLARD: Jim Dillard, Altria Client 5 Services. Richard, you just brought up something 6 really interesting that I hadn't thought about 7 until you started talk about it. But the public 8 availability of data that the public has never had 9 available to it at this point, can you talk a 10 little bit about what were some of the areas that 11 you were thinking about as you went through some of 12 those lists and kind of came up with the questions? 13 What were some of the thoughts Medtronic was having 14 about what could some of the downsides be about 15 having this data publicly available, where anybody 16 could access it? 17 I only bring that up -- and I'm not trying 18 to bring up a whole other topic, but we're sort of 19 faced with that in the tobacco industry, which is 20 we're getting ready to publish harmful and 21 potentially harmful constituent data for the 22 public. And so it would be a good sort of</p>

<p style="text-align: right;">Page 297</p> <p>1 conversation and a parallel to just hear from you, 2 what are the struggles that you've thought of. 3 DR. KUNTZ: Our biggest concern are litigant 4 firms. And we know that there's a profit by 5 litigant firms to try to take data and view it in a 6 view that would be their business model for making 7 profit, and we've seen that happen in the past. 8 So when we look at the fact that 9 biostatistical standards are evolving, the 10 statistical -- let me give you an example. I can 11 tell you that the systematic reviews are not 12 completely harmonized. These are two outstanding 13 groups that did reviews of all this stuff, and they 14 have slightly different conclusions, at least the 15 first draft I saw. 16 So we know that methodologies, even in the 17 best intent by the most talented individuals, often 18 won't be fully coherent on that level. So if you 19 look at the next level spectrum, which is nefarious 20 manipulation, that data up front, that's the 21 biggest downside by far. 22 We don't fear good methodology finding</p>	<p style="text-align: right;">Page 299</p> <p>1 against -- who don't have the capabilities, and 2 that's all good. But we've seen behavior that 3 might not be consistent with trying to find the 4 truth all the time, and that's our biggest concern. 5 MS. DILLEY: I just want to thank you, Mark, 6 and Eric, who's not here any longer, for your 7 comments and also taking questions and answers, so 8 thank you. 9 (Applause.) 10 Adjournment 11 MS DILLEY: We're going to conclude today's 12 session. I just wanted to give you a sense of 13 tomorrow. 14 On your agenda, we start at 8:30 in the 15 morning, and we'll go over some of the details of 16 how the day is going to go. Then we have the 17 public comment period from 9:00 to 9:30. And then 18 we'll start the next panel in Challenges in 19 Conducting Industry-Sponsored Research with another 20 set of panelists. 21 We have two before a break and then, again, 22 I just want to remind people that that break is</p>
<p style="text-align: right;">Page 298</p> <p>1 problems in our products. We want to know that 2 just as well as anybody does. We don't fear the 3 universities working with us and the FDA and other 4 people getting access to it. We fear individuals 5 who have a business model to make money by 6 potentially using data that they can manipulate. 7 That's the biggest concern. 8 One could say, "Well, as long as they make 9 their methods transparent, we can be able to 10 challenge them." In our field, the first two or 11 three sentences of a result are all you get to 12 listen to. It's often you don't get into the 13 methods all the time, especially when it becomes a 14 headline on a paper. And we know the thresholds 15 that get into media often aren't reviewed by 16 statistical editors at certain media outlets. 17 So these are the biggest concerns we have, 18 and these are shared by all of the other 19 perspectives I think up front here because of this. 20 And I don't want to taint litigant firms. They 21 serve people, no question, that there are 22 individuals who need to be protected to fight</p>	<p style="text-align: right;">Page 300</p> <p>1 15 minutes, not 45 minutes. So we'll start back up 2 at 10:15, and then go to 11:45, where we'll switch 3 gears to Q&A, and some concluding comments, and 4 close the session at 1:00, no later than 1:00. 5 So have a good evening and we'll see you 6 tomorrow. 7 (Whereupon, at 3:56 p.m., the meeting was 8 adjourned.) 9 10 11 12 13 14 15 16 17 18 19 20 21 22</p>

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